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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: 1/05/2010

SUBJECT: **Abamectin:** Review of developmental neurotoxicity study (MRID 46727401, -02, & -03) (2005 study)

PC Code: 122804
Decision No.: NA
Petition No.: NA
Risk Assessment Type:NA
TXR No.: 0054054
MRID No.: 46727401, -02, & -03

DP Barcode: 325739
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: NA
40 CFR: NA

FROM: Whang Phang, PhD
Toxicologist
RAB /HED (P7509P)

THROUGH: Paula Deschamp, Branch Chief
RAB /HED (P7509P)

TO: Thomas Harris, Risk Manager Review
Risk Management Team 07
RD (P7509P)

ACTION REQUESTED: Review the developmental neurotoxicity study in rats on abamectin (MRID 46727401, -02, & -03).

RESULTS and DISCUSSION: The developmental neurotoxicity study on abamectin in rats has been reviewed and the results and conclusion are presented below.

In a developmental neurotoxicity study (MRIDs 46727403, 46727402, and 46727401) Abamectin (96.2% a.i. on dry basis; Batch No.: VS094KO) in sesame oil was administered via gavage (10 mL/kg) to pregnant Alpk:AP$_f$SD rats (30/dose) from gestation day (GD) 7 through lactation day (LD) 22 at doses of 0, 0.12, 0.20, or 0.40 mg/kg/day. The pups were not directly

RECVD 1/12/2010

dosed. Dams were allowed to deliver naturally and were killed at weaning on LD 29. On post-natal day (PND) 5, litters were standardized to 8 pups/litter; the remaining offspring and dams were sacrificed and not examined further. Subsequently, 1 pup/sex/litter/group (at least 10 pups/sex/dose when available) were allocated to the following subsets: Subset 1: functional observational battery (FOB) on PND 5, 12, 22, 36, 46, and 61; motor activity on PND 14, 18, 22, and 60; and brain weight and neuropathology on PND 63. Subset 2: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 24 and 27; and brain weight and neuropathology on PND 63. Subset 3: FOB on PND 5 and 12; auditory startle on PND 23 and 61 (for animals not sacrificed on PND 12); and brain weight and neuropathology on PND 12. Subset 4: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 59 and 62.

Maternal toxicity: There were no effects of treatment on mortality, clinical signs, functional observational battery parameters, body weights, body weight gains, food consumption, reproductive performance, or gestation length.

The maternal LOAEL was not observed. The maternal NOAEL is 0.4 mg/kg/day.

Offspring toxicity: No treatment-related effects were observed on litter parameters (number born live, number born dead, sex ratio (% male), mean litter size, live birth index, and viability index), clinical signs, FOB parameters, motor activity, auditory startle reflex, learning and memory, sexual maturation, brain weight, or gross or microscopic pathology.

On the day of weaning (PND 29), minor decreases ($p<=0.05$) in pup body weights of 5-7% were observed at 0.40 mg/kg/day. Pup body weights continued to be decreased ($p<=0.01$) by 5-6% in the males and by 8-10% in the females throughout the post-weaning interval (PND 36-63).

The offspring LOAEL is 0.4 mg/kg/day, due to decreased body weights in both sexes. The NOAEL is 0.2 mg/kg/day.

There was no evidence of neurotoxicity in the offspring.
This study is classified as acceptable/non-guideline, and the results of this study should be considered together with those of a follow-up study conducted in 2007 (MRID 47116201).

MRID Summary Table

Study Type	MRID	Comments
developmental neurotoxicity study in rats	46727403, -02, & -01	The study is classified as acceptable non-guideline

DATA EVALUATION RECORD

ABAMECTIN

Study Type: §83-6, Developmental Neurotoxicity Study in Rats

Work Assignment No. 3-1-113 A and B (MRID 46727403, 46727402, and 46727401)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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Toxicology Branch, Health Effects Division (7509P) **Date:** 10/22/09
Work Assignment Manager: Myron S. Ottley, Ph.D. **Signature:**
Registration Action Branch 3, Health Effects Division (7509P) **Date:** 10/2/09

Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Developmental Neurotoxicity Study - Rat; OPPTS 870.6300 (§83-6); OECD 426 (draft)

PC CODE: 122804 **DP BARCODE:** D325739
TXR#: 0054054

TEST MATERIAL (PURITY): Abamectin technical (86.2% a.i., or 96.2% on a dry basis)

SYNONYMS: Avermectin A1a, 5-O-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)-, mixture with 5-O-demethylavermectin A1a; MK 936

CITATION: Moxon, M.E. (2005) Abamectin: Developmental neurotoxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Project Id.: CTL Study No. RR1048-REG, Syngenta No. T000967-05, December 16, 2005. MRID 46727403. Unpublished.

Chivers, S. (2005) Abamectin: Preliminary developmental neurotoxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Study Id.: CTL Study No. RR0966, May 10, 2005. MRID 46727402. Unpublished.

Gledhill, A. (2005) Avermectin B_{1a}: Comparative maternal and pup exposure following dietary and gavage dosing in the rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Study Id.: CTL No. UR0795, April 28, 2005. MRID 46727401. Unpublished.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, PO Box 18300, Greensboro, NC

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRIDs 46727403, 46727402, and 46727401) Abamectin (96.2% a.i. on dry basis; Batch No.: VS094KO) in sesame oil was administered via gavage (10 mL/kg) to pregnant Alpk:AP$_f$SD rats (30/dose) from gestation day (GD) 7 through lactation day (LD) 22 at doses of 0, 0.12, 0.20, or 0.40 mg/kg/day. The pups were not directly dosed. Dams were allowed to deliver naturally and were killed at weaning on LD 29. On post-natal day (PND) 5, litters were standardized to 8 pups/litter; the remaining offspring and dams were sacrificed and not examined further. Subsequently, 1 pup/sex/litter/group (at least 10 pups/sex/dose when available) were allocated to the following

subsets: Subset 1: functional observational battery (FOB) on PND 5, 12, 22, 36, 46, and 61; motor activity on PND 14, 18, 22, and 60; and brain weight and neuropathology on PND 63. Subset 2: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 24 and 27; and brain weight and neuropathology on PND 63. Subset 3: FOB on PND 5 and 12; auditory startle on PND 23 and 61 (for animals not sacrificed on PND 12); and brain weight and neuropathology on PND 12. Subset 4: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 59 and 62.

Maternal toxicity: There were no effects of treatment on mortality, clinical signs, functional observational battery parameters, body weights, body weight gains, food consumption, reproductive performance, or gestation length.

The maternal LOAEL was not observed. The maternal NOAEL is 0.4 mg/kg/day.

Offspring toxicity: No treatment-related effects were observed on litter parameters (number born live, number born dead, sex ratio (% male), mean litter size, live birth index, and viability index), clinical signs, FOB parameters, motor activity, auditory startle reflex, learning and memory, sexual maturation, brain weight, or gross or microscopic pathology.

On the day of weaning (PND 29), minor decreases ($p<=0.05$) in pup body weights of 5-7% were observed at 0.40 mg/kg/day. Pup body weights continued to be decreased ($p<=0.01$) by 5-6% in the males and by 8-10% in the females throughout the post-weaning interval (PND 36-63).

The offspring LOAEL is 0.4 mg/kg/day, due to decreased body weights in both sexes. The NOAEL is 0.2 mg/kg/day.

There was no evidence of neurotoxicity in the offspring.
This study is classified as acceptable/non-guideline, and the results of this study should be considered together with those of a follow-up study conducted in 2007 (MRID 47116201).

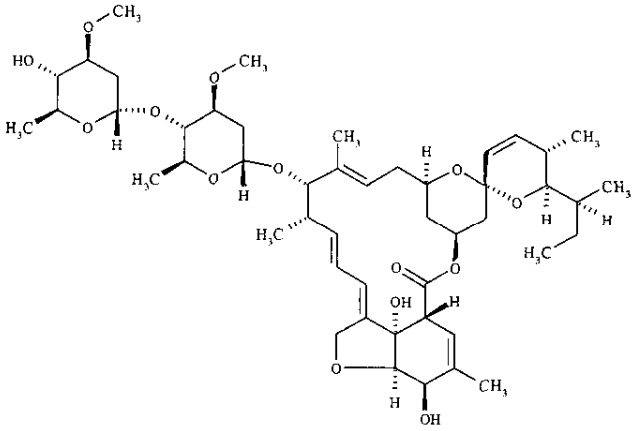
COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Abamectin technical

Description: White powder
Batch No.: VS094KO
Purity: 86.2% a.i. (96.2% on a dry basis)
Stability of compound: It was stated that stability was determined in another study; however, the results were not provided.
CAS #: 71751-41-2
Structure:



2. Vehicle: Sesame oil

3. Test animals

Species: Rat
Strain: Alpk:AP$_f$SD (Wistar-derived)
Age and group mean weight at initiation of treatment: Females 10-12 weeks of age weighing 245-257 g
Source: Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
Housing: Parent females and litters were housed until weaning in solid plastic cages with woodflake bedding and paper for nesting material. Then, the selected F1 rats were housed by sex and litter in wire mesh cages
Diet: CT1 diet (Special Diet Services Limited, Stepfield, Witham, Essex, UK), *ad libitum*
Water: Tap water, *ad libitum*
Environmental conditions
Temperature: 22±3°C
Humidity: 30-70%
Air changes: 15/h
Photoperiod: 12 h light/12 h dark
Acclimation period: 6 days

B. STUDY DESIGN

1. **In life dates:** Start: Not reported End: Not reported

2. **Study schedule:** The P females were administered the test substance daily via gavage (10 mL/kg) from gestation day (GD) 7 until lactation day (LD) 22 (inclusive). The pups were not directly dosed. On post-natal day (PND) 5, the litters were standardized to 8 pups/litter (with equal sexes where possible) to reduce the variability. The pups retained in each litter were selected at random from those available. Pups that were not selected for the F1 generation were killed and discarded on PND 5. The dams were killed at weaning (PND 29) and were discarded. One F1 rat/sex/litter was killed on PND 12 and PND 63, and their brains were fixed and weighed. Ten rats/sex/dose were killed on PND 63, brain weights were measured, and tissues were taken for microscopic analysis. All remaining pups were killed and discarded at PND 63.

3. **Mating procedure:** The animals were time mated by the animal supplier. The day on which sperm was detected in a vaginal smear was designated as GD 1, and these females were delivered to the testing laboratory. Twenty females were supplied on each of 6 days. Further details were not provided. The day on which parturition occurred was designated as LD 1. Parent females and litters were housed together until weaning in solid plastic cages with woodflake bedding and paper for nesting material. The selected F1 rats were then housed by sex and litter in wire mesh cages.

4. **Animal assignment:** Pregnant females were randomly assigned to dose groups as indicated in Table 1. Dams were assigned to functional observation testing as shown. Pups that were not selected for the F1 group, animals found dead, and animals requiring euthanasia were killed and discarded without examination. Offspring were assigned to testing subgroups at the time of litter standardization on PND 5. Animals were allocated to the following subsets (1 pup/sex/litter): Subset 1: functional observational battery (FOB) on PND 5, 12, 22, 36, 46, and 61; motor activity on PND 14, 18, 22, and 60; and brain weight and neuropathology on PND 63. Subset 2: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 24 and 27; and brain weight and neuropathology on PND 63. Subset 3: FOB on PND 5 and 12; auditory startle on PND 23 and 61 (for animals not sacrificed on PND 12); and brain weight and neuropathology on PND 12. Subset 4: FOB on PND 5, 12, 22, 36, 46, and 61; water maze on PND 59 and 62.

TABLE 1. Study Design [a]

Experimental parameter	Dose (mg/kg/day)				Subset [b]
	0	0.12	0.20	0.40	
Maternal animals					
No. of maternal animals assigned	30	30	30	30	NA
FOB (GD 10 and 17, LD 2 and 9)	29	30	30	30	NA
Offspring					
Detailed clinical/FOB (PND 5 and 12)	11-13/sex	12/sex	14-15/sex	13-14/sex	1, 2, 3, 4
Detailed clinical/FOB (PND 22, 36, 46, and 61)	11-13/sex	12/sex	14-15/sex	13-14/sex	1, 2, 4
Motor activity (PND 14, 18, 22, and 60)	12/sex	12/sex	14-15/sex	13-14/sex	1
Auditory startle habituation (PND 23 and 61)	11-12/sex	11-12/sex	14-15/sex	12-13/sex	3
Learning and memory (water maze; PND 24 and 27)	24/sex	24/sex	29/sex	27/sex	2
Learning and memory (water maze; PND 59 and 62)	22-24/sex	23-24/sex	25-29/sex	26-27/sex	4
Brain weight					
PND 12	12/sex	12/sex	14-15/sex	13-14/sex	3 [c]
PND 63 (perfused and not perfused)	12/sex	12/sex	14-15/sex	13-14/sex	1, 2
Neuropathology					
PND 12 (brain only)	10/sex	0/sex	10/sex	10/sex	3 [c]
PND 63	10/sex	0/sex	0/sex	10/sex	1, 2

a Data were obtained from pages 20-24, 43-66, and 89-177 of MRID 46727403. Offspring were selected one male or one female from each litter for use in the FOB, motor activity, startle and water maze tests.

b Selected pups were randomly assigned numbers. The first (lowest number) male and female from each litter were assigned to Subset 1. The second male and female from each litter was assigned to Subset 2, and so on.

c Excludes animals selected for auditory startle habituation.

5. **Dose-selection rationale:** The Sponsor stated that the lowest and highest dose concentrations were chosen based on the no observed adverse effect level and the highest dose concentration used in a multigeneration reproductive toxicity study: (Gordon, 1984). Further information from this study was not provided. A range-finding study in rats (MRID 46727402) was submitted concurrently. This study is summarized in Appendix 1 of this DER.

6. **Dosage preparation, administration, and analysis:** All doses were administered once daily to maternal animals by gavage on GD 7 through LD 22 (inclusive). The gavage dose was administered in a volume of 10 mL/kg bw. Dose and volume calculations were based on the body weight of each individual rat, measured daily during the dosing period. Dose formulations were prepared approximately weekly, without adjustment for purity, by mixing appropriate amounts of the test compound in sesame oil. Dose formulations were stored at room temperature. The first and last batches of the dose formulations were analyzed for concentration. The lowest and highest concentrations of the second and last batches were analyzed for homogeneity (top, middle, bottom). It was stated that the chemical stability of abamectin in sesame oil at concentrations of 0.01 mg/mL and 1 mg/mL at room temperature was established in another study (CTL/WK0587/Regulatory/Report); however, the results were not reported.

Results:

Homogeneity (range as % CV): 11.5% in the 0.012 mg/mL second batch and 0.0-6.8% for all other measurements

Concentration (range as % of nominal): 116.7% in the 0.012 mg/mL first batch, but 90.0-110.0% for all other measurements

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

C. OBSERVATIONS

1. In-life observations

a. **Maternal animals:** The dams were checked for mortality twice daily. Clinical observations of the dams were conducted cage-side during acclimation and twice daily during the study. Detailed observations were recorded on GD 1, prior to dosing on GD 7 through LD 22, LD 29, and prior to termination.

On GD 10 and 17 and LD 2 and 9, all females were observed outside the home cage by a technician who was unaware of each rat's dose group. This observation was performed before dosing the animals. It was not stated if the same technicians observed the animals throughout testing. Severity codes for observations were reported as no abnormalities detected, slight, or present. The following functional observations were reported:

	FUNCTIONAL OBSERVATIONS
X	Signs of autonomic function, including: 1) Ranking of degree of lacrimation and salivation, with range of severity scores from none to severe 2) Presence or absence of piloerection and exophthalamus, 3) Ranking or count of urination and defecation, including polyuria and diarrhea 4) Pupillary function such as constriction of the pupil in response to light, or a measure of pupil size 5) Degree of palpebral closure, e.g., ptosis.
X	Description, incidence, and severity of any convulsions, tremors, or abnormal movements.
X	Description and incidence of posture and gait abnormalities.
X	Description and incidence of any unusual or abnormal behaviors, excessive or repetitive actions (stereotypies), emaciation, dehydration, hypotonia or hypertonia, altered fur appearance, red or crusty deposits around the eyes, nose, or mouth, and any other observations that may facilitate interpretation of the data.

Further details concerning the functional observational battery were not provided.

The body weight of each parent female was recorded on GD 1, immediately prior to dosing on GD 7 through LD 22, LD 29, and prior to termination. Food consumption was calculated (g/rat/day) for GD 1-7, 7-15, and 15-22, and LD 1-5, 5-8, 8-12, 12-15, 15-18, 18-21, and 21-23.

b. Offspring

1. **Litter observations:** The day of completion of parturition was designated as PND 1. On PND 1 and 5, the sex, weight, and clinical condition of each pup were recorded. Cage-side observations for mortality, morbidity and clinical signs were made at least once daily; the F1 animals were also observed when weighed.

   On PND 5, the litters were standardized to 8 pups/litter (with equal sexes where possible) to reduce the variability. The pups retained in each litter were selected at random from litters of 7-8 pups with at least 3 pups of each sex. Pups that were not selected for the F1 generation were killed and discarded. Body weights were record on PND 1, 5 (pre-cull), 5 (post-cull), 12, 18, 22, and 29.

2. **Developmental landmarks:** Beginning on PND 41, all male offspring were examined daily for preputial separation. Beginning on PND 29, all female offspring were examined daily for vaginal patency. The age of onset was recorded, and body weights were recorded for each rat on the day of sexual maturation.

3. **Postweaning observations:** After weaning on PND 29, cage-side observations for mortality, morbidity and clinical signs were made at least once daily, and also when the animals were weighed. Body weights were record on PND 36, 43, 50, and 57, at sexual maturation, and at termination.

4. **Neurobehavioral evaluations:** Observations and the schedule for those observations are summarized as follows from the report.

i. **Functional observational battery (FOB):** On PND 5 and 12 (all Subsets) and PND 22, 36, 46, and 61 (Subsets 1, 2, and 4), selected animals (one male or female from each litter) were examined outside of the home cage. The same parameters assessed in the maternal FOB were examined in the offspring by an individual who was unaware of each rat's dose group. Additional information was not provided.

ii. **Motor activity testing:** Motor activity measurements were performed on Subset 1 (one male or female from each litter) on PND 14, 18, 22, and 60. Tests were recorded in a separate room (environmental conditions not provided). An automated activity recording apparatus (make and source not provided) recorded small and large movements as an activity count. Each assessment was divided in into 10 scans of 5 minute duration. Treatment groups were counterbalanced across cage/device number. When trials were repeated, each animal was returned to the same activity monitor. Further details were not provided.

iii. **Auditory startle reflex habituation:** Auditory startle response and habituation testing was performed on Subset 3 (one male or female from each litter) on PND 23 and 61. An automated system (make and source not provided) was used to measure the mean response amplitude and time to maximum amplitude within each block of 10 trials. There were 5 blocks of 10 trials per session on each day of testing. Further details were not provided.

iv. **Learning and memory testing:** Selected animals (one male or one female from each litter) were tested for associative learning and memory. The test used a "Y"-shaped water maze with one escape ladder. The time taken by the pup to find the escape ladder was recorded for each trial. Animals were given 6 trials on PND 24 (Subset 2) or 59 (Subset 4). Additionally, a straight channel was used to evaluate swimming speed. Each animal completed one trial in the straight channel immediately following the six trials in the "Y"-shaped water maze. Three days later (PND 27 or 62) the same animals were retested using the same procedures. Learning was assessed by comparing the time required to complete the maze on trial 6 vs trial 1 in the learning phase. Memory was assessed by comparing the time required to complete the maze in the first trial in the memory phase to the time required in the learning phase. Proportions of successful trials were calculated based on the trial being completed in less than 3, 4, 5, 6, 7, 8, 9, or 10 seconds or 1.0x, 1.5x, or 2.0x the time required to complete the straight channel. Further details were not provided.

5. **Cholinesterase determination:** Cholinesterase activity was not assessed in this study.

6. **Pharmacokinetic data:** A concurrently submitted study (MRID 46727401) evaluated the pharmacokinetics of avermectin $B1_a$. A summary of this study is presented in Appendix 2 of this DER.

2. **Postmortem observations**

a. **Maternal animals:** P females were killed by overexposure to halothane Ph. Eur. vapor followed by exsanguination. Females with litters not required for selection, with total litter loss, and parents at PND 29 were killed and discarded without examination. Females that failed to litter were examined macroscopically, and the uterus was examined to confirm pregnancy status.

b. **Offspring:** Any animal found dead and the following terminated offspring were not examined pathologically: any pups that required euthanasia, pups not selected for the F1-generation on PND 5, and F1 pups not selected for brain weight measurement.

On PND 12, Subset 3 rats (one male or one female from each litter) were killed by exposure to carbon dioxide, and the brain was immediately exposed and immersion fixed in 10% neutral buffered formol saline. The brains were weighed after approximately 24 hours fixation. The brains from control, 0.2, and 0.4 mg/kg/day groups were embedded in paraffin wax, sectioned into 7 levels, stained routinely with hematoxylin and eosin, and examined microscopically.

On PND 63, Subsets 1 and 2 rats (one male or one female from each litter) were processed as on PND 12, except that the brain was fixed and stored after weighing. Also, on PND 63, an additional 10 rats/sex/group were deeply anesthetized by intraperitoneal injection of sodium pentobarbitone and killed by perfusion fixation with formol saline. The rats were perfused with a volume of fixative approximately equivalent to their estimated bodyweight.

The brain was removed and weighed, and the following tissues were taken and preserved in unspecified fixatives.

	CENTRAL NERVOUS SYSTEM		PERIPHERAL NERVOUS SYSTEM
X	**BRAIN**		**SCIATIC NERVE**
	Forebrain		Mid-thigh
	Center of cerebrum	X	Sciatic notch
	Midbrain		
	Cerebellum		**OTHER**
	Pons		Sural nerve
	Medulla oblongata	X	Tibial nerve (proximal and distal)
	SPINAL CORD		Peroneal nerve
X	Cervical swelling	X	Lumbar dorsal root fibers
X	Lumbar swelling	X	Lumbar dorsal root ganglion
	OTHER	X	Lumbar ventral root fibers
	Gasserian ganglion	X	Cervical dorsal root ganglion
	Trigeminal nerves	X	Cervical dorsal root fibers
X	Optic nerve	X	Cervical ventral root fibers
X	Eyes	X	Gastocnemius muscle

Tissues from the control and 0.4 mg/kg/day groups were processed. The brain was processed as on PND 12. The following tissues were trimmed, embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin: transverse sections of the gastrocnemius muscle, eye with retina and optic nerve, spinal cord at cervical and lumbar swellings with the dorsal root ganglia and dorsal and ventral spinal root fibers; longitudinal sections of the spinal cord at the cervical and lumbar swellings. The following tissues were embedded in resin and semi-thin sections cut and stained with toluidine blue: transverse and longitudinal sections of the proximal sciatic nerve, proximal tibial nerve, and distal tibial nerve (tibial nerve calf muscle branches). All processed tissues were examined microscopically. The Sponsor stated that procedural deficiencies that affected the morphometric data had no impact on the qualitative evaluation of neuropathological change.

Brain morphometric analysis was done for control and 0.4 mg/kg/day groups terminated at 12 and 63 days of age. However, key procedural deficiencies were identified, which the Sponsor concluded made this data uninterpretable; therefore, these data were not included in the Study Report.

D. DATA ANALYSIS

1. **Statistical analyses:** Data were analyzed using SAS. The data were tested ($p \leq 0.05$ and ≤ 0.01) using the following statistical methods:

Parameter	Statistical Methods
Gestation body weights	Analysis of covariance (ANCOVA) on GD 7 body weight
Post partum body weights	One-way analysis of variance (ANOVA) with Dunnett's test for comparison of treatment groups with controls, using the litter as the statistical group. (JMP 7.0.1, SAS Institute, Inc., Cary, NC)
Gestation food consumption during dosing and *post partum*; gestation, length, litter size, initial (PND 1) mean pup body weight, and total litter weights; PND 5 litter-based mean body weights for F1 animals; motor activity measurements, the maximum amplitude and time to maximum amplitude in the startle response tests, the litter based mean time to preputial separation or vaginal opening, and mean litter bodyweights at the time of developmental landmarks	Analysis of variance (ANOVA); for body weight and food consumption analyses, sexes were evaluated separately and whole litter losses were excluded
Pup body weights after PND 1	ANCOVA on PND 1, sexes separate
Proportion of litters with gestation length <22, 22, and >22 days and the proportion of whole litter losses in each treated group; proportion of pups born live, the proportion of pups surviving, the proportion of litters with all pups born live, the proportion of litters with all pup surviving and the proportion of male pups	Fisher's Exact Test
Live born pups, pre-cull pup survival, and pup sex	Percentages were considered by ANOVA following double arcsine transformation of Freeman and Tukey.
Mean body weight in F1 animals after PND 5	ANCOVA on PND 5 bodyweights

Assuming that the assumptions of parametric analyses were verified prior to parametric analyses, the statistical analyses were considered appropriate.

2. **Indices**

a. **Reproductive indices:** The percentage of dams with gestation lengths <22 days, 22 days, and >22 days were reported.

b. **Offspring viability indices:** The percentage of pups born live (live birth index), pups surviving at PND 5, whole litter losses, and male pups at PND 1 and 5 were reported. Additionally, the proportion of litters with all pups surviving until PND 5 was also reported. The reviewers calculated the viability index as the mean litter size on PND 5 x 100/ mean litter size on PND 1.

3. **Positive control data:** Positive control data for neurobehavioral testing and neuropathology were not presented.

II. RESULTS

A. PARENTAL ANIMALS

1. **Mortality, clinical signs, and functional observations:** No treatment-related effects were observed on mortality, clinical signs, or functional observations. One control female and one 0.4 mg/kg/day female were killed on GD 25, because they failed to litter. Both females were found not to have been pregnant at necropsy. One 0.12 mg/kg/day female was killed after a total litter loss. Dams (1-5/group, unrelated to dose) were killed because they produced an insufficient number of pups (<3 males and 3 females in a litter or <7 pups).

2. **Body weight and food consumption:** Selected group mean body weights and food consumption values for pregnant and nursing dams are presented in Table 2. Treatment-related increases ($p \leq 0.05$) in body weight were observed in the 0.20 and 0.40 mg/kg/day P females. These increases were observed throughout gestation beginning on GD 9 at 0.20 mg/kg/day (↑6-7%) and on GD 8 at 0.40 mg/kg/day (↑3-6%). Transient increases ($p \leq 0.05$) in body weight were also observed from GD 9-13 at 0.12 mg/kg/day (↑3-4%). Increases in body weight gain (calculated by reviewers) were observed on GD 7-22 and 1-22 (↑10-16%) in the 0.20 and 0.40 mg/kg/day P females. Concurrent increases ($p \leq 0.05$) in food consumption were observed on GD 7-15 and 15-22 and LD 1-5 (↑8-14%). Other increases ($p \leq 0.05$) in food consumption were noted, but were minor and unrelated to dose. Although treatment-related, these minor increases in body weights and body weight gains (and concurrent effect on food consumption) were not considered adverse.

   Increased ($p \leq 0.05$) body weights were observed in all treated groups on LD 1 and 2 (↑6-11%), but thereafter an increase ($p \leq 0.05$) was only observed in the 0.20 mg/kg/day P females on LD 3 (↑10%). A concurrent increase ($p \leq 0.05$) in food consumption was observed on LD 1-5 (↑12-14%) in the 0.20 and 0.40 females. Decreases in body weight gain were observed in all treated P female groups at LD 1-29 (↓61-83%); however, as body weights were similar in all groups on LD 29, these findings were not considered adverse.

TABLE 2. Mean (±SD) maternal body weight and food consumption [a]

Observations/study day	Dose (mg/kg/day)			
	Control	0.12	0.20	0.40
Gestation				
Mean body weight (g)				
GD 1	244.9±17.1	253.2±19.5	257.3±22.6	251.5±22.8
GD 7	280.6±16.3	286.9±21.3	294.4±21.8	286.1±24.7
GD 8	283.3±16.5	291.0±21.1	299.1±22.4	292.5±25.8** (↑3)
GD 9	286.2±16.2	296.4±20.7** (↑4)	304.9±21.9** (↑7)	298.2±26.5** (↑4)
GD 11	299.6±16.9	308.9±22.9* (↑3)	318.7±21.8** (↑6)	312.0±28.1** (↑4)
GD 13	312.2±17.5	322.2±22.0* (↑3)	333.2±22.9** (↑7)	325.7±28.0** (↑4)
GD 19	368.8±21.4	379.9±26.2	394.5±25.4** (↑7)	391.4±33.6** (↑6)
GD 22	411.9±26.2	423.7±33.1	441.4±28.7* (↑7)	438.2±39.3** (↑6)
Mean body weight gain (g)				
GD 7-22[b]	131.3	136.8	147.0 (↑12)	152.1 (↑16)
GD 1-22[b]	167.0	170.5	184.1 (↑10)	186.7 (↑12)
Mean food consumption (g/animal/day)				
GD 7-15	21.3±2.6	22.3±2.6	24.2±2.9** (↑14)	23.1±2.8** (↑8)
GD 15-22	21.8±3.3	23.0±3.1	24.7±3.3** (↑13)	24.9±3.2** (↑14)
Lactation				
Mean body weight (g)				
LD 1	319.2±20.5	338.1±28.0** (↑6)	346.5±26.7** (↑9)	342.9±31.6** (↑7)
LD 2	314.8±22.2	337.4±23.2* (↑7)	348.6±25.3** (↑11)	342.3±32.1* (↑9)
LD 3	318.8±24.3	339.7±23.3	350.8±26.2* (↑10)	343.8±31.1
LD 29	342.5±22.6	347.3±22.6	350.5±20.5	349.3±25.1
Mean body weight gain (g)				
LD 1-29[b]	23.3	9.2 (↓61)	4.0 (↓83)	6.4 (↓73)
Mean food consumption (g/animal/day)				
LD 1-5	25.8±5.4	28.1±5.3	28.9±4.9* (↑12)	29.4±3.5** (↑14)

a Data (n=23-30) were obtained from pages 67-75 of MRID 46727403. Except for GD 1, statistical analysis was performed on the adjusted means (ANCOVA analysis on GD 7). Percent difference from control (calculated by reviewers) is presented parenthetically.

b Calculated by reviewers from data presented in this table.

* Statistically different from control, $p \leq 0.05$.

** Statistically different from control, $p \leq 0.01$.

3. **Reproductive performance:** No treatment-related effects were observed on reproductive performance (Table 3).

TABLE 3. Reproductive performance [a]

Observation	Dose (mg/kg/day)			
	Control	0.12	0.20	0.40
Number mated	30	30	30	30
Number of litters	29	30	30	29
Intercurrent deaths[b]	0	0	0	0
Mean (±SD) gestation duration (days)	22.0±0.0	22.1±0.3	22.0±0.2	22.0±0.0
Incidence of dystocia[c]	0	0	0	0

a Data were obtained from pages 22 and 76-77 in MRID 46727403.

b One control and one female were sacrificed at GD 29 and were found to be not pregnant.

c No incidence of dystocia was noted in the clinical observations.

4. **Maternal postmortem results:** Dams were not examined grossly or histologically except to verify pregnancy state.

B. OFFSPRING

1. **Viability and clinical signs:** No treatment-related effects were observed on the viability (Table 4) or clinical signs (including FOB) of the offspring from the time the pups were born until their scheduled sacrifice. One 0.20 mg/kg/day male and one 0.40 mg/kg/day female were found dead on PND 51 and 40, respectively, but these deaths were not considered treatment-related.

TABLE 4. Litter size and viability [a]

Observation	Dose (mg/kg/day)			
	Control	0.12	0.20	0.40
Total number born	373	356	377	388
Number born live	373	352	374	388
Number born dead	0	4	3	0
Sex Ratio Day 1 (% %)	47.7±14.6	50.4±19.6	51.5±13.3	51.0±12.7
# Survivors Days 1-5 (%)	96.8±12.0	99.5±1.8	97.9±6.7	98.0±3.8
Mean litter size [b]:				
Day 1	12.9±2.7	11.7±3.9	12.5±2.9	13.4±2.5
Day 5 [c]	12.4±3.0	11.7±3.8	12.3±3.1	13.1±2.5
Live birth index	100	98.9	99.2	100
Viability index [d]	96.1	100.0	98.4	97.8

a Data obtained from pages 77-81 in MRID 46727403.
b Excluding whole litter losses (of which 1 occurred at 0.12 mg/kg/day and at no other dose)
c Before standardization (culling).
d Calculated by the reviewers from data in this table as the mean litter size on PND 5 x 100/ mean litter size on PND 1

2. **Body weight:** Minor increases ($p \leq 0.05$) in offspring body weights were noted during pre-weaning in both sexes (↑4-11%), but these increases were unrelated to dose (Table 5). On the day of weaning (PND 29), minor decreases ($p \leq 0.05$) in body weights were observed in the 0.40 mg/kg/day males and females (↓5-7%).

TABLE 5. Mean (±SD) pre-weaning pup body weights (g) [a]

PND	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
	Males			
1	6.0±0.6	6.3±0.7	6.3±0.5* (↑5)	6.2±0.4
5 [b]	9.4±1.5	10.2±1.0** (↑9)	10.3±1.1* (↑10)	9.9±0.9
5 [c]	9.4±0.9	10.2±0.9** (↑9)	10.4±1.0** (↑11)	10.1±0.9* (↑7)
8	15.2±1.4	16.4±1.2* (↑8)	16.6±1.5** (↑9)	16.1±1.3
12	24.3±2.1	26.1±1.5** (↑7)	26.3±2.0** (↑8)	25.7±2.0* (↑6)
15	32.7±2.2	35.0±2.1** (↑7)	35.3±2.6** (↑8)	34.6±2.2* (↑6)
22	52.8±3.3	56.0±3.3** (↑6)	56.6±3.1** (↑7)	55.4±3.1* (↑5)
29	91.8±4.6	92.7±5.8	92.9±4.0	87.3±4.5* (↓5)
	Females			
1	5.7±0.6	6.1±0.7** (↑7)	5.9±0.3	5.8±0.3
5 [b]	9.3±1.2	10.1±1.1* (↑9)	9.6±0.9	9.5±0.9
5 [c]	9.2±1.0	9.9±1.0* (↑8)	9.7±1.0	9.7±0.9
8	14.9±1.4	16.0±1.1** (↑7)	15.7±1.5	15.6±1.1
12	23.8±2.3	25.7±1.6** (↑8)	25.1±2.0	24.8±1.6
15	32.4±2.2	34.5±2.0** (↑6)	33.7±2.6	33.6±1.8
22	52.0±3.1	54.8±2.9** (↑5)	53.9±3.6	54.0±2.5* (↑4)
29	87.2±4.7	87.1±4.8	84.4±4.9	81.1±4.5** (↓7)

a Data (n=24-29) were obtained from pages 83 and 125-127 in MRID 46727403. Statistical analysis was performed by the reviewers (ANOVA followed by Dunnett's test). Percent difference from control (calculated by reviewers) is presented parenthetically.
b Before standardization (culling).
c After standardization (culling).
* Statistically different from control, $p \leq 0.05$
** Statistically different from control, $p \leq 0.01$

At 0.40 mg/kg/day, pup body weights were decreased ($p \leq 0.01$) by 5-6% in the males, and by 8-10% in the females throughout the post-weaning interval (PND 36-63; Table 6). Minor decreases ($p \leq 0.05$) were also observed in the 0.20 mg/kg/day females on PND 36 (↓5%) and PND 63 (↓4%).

TABLE 6. Mean (±SD) post-weaning pup body weights (g) [a]				
PND	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
	Males			
36	145.0±5.5	144.9±8.4	146.3±7.0	136.7±7.0** (↓6)
43	199.9±8.6	199.3±9.8	200.3±9.7	189.2±10.1** (↓5)
50	257.2±9.7	257.6±12.6	257.2±11.9	244.1±13.6** (↓5)
57	312.7±12.4	310.8±15.3	311.5±16.0	293.7±16.4** (↓6)
63	346.1±15.8	343.5±18.2	342.2±17.9	323.7±17.1** (↓6)
	Females			
36	128.5±6.5	126.3±5.8	122.7±7.5** (↓5)	115.4±6.1** (↓10)
43	161.4±8.2	158.8±8.8	155.9±9.8	147.5±8.2** (↓9)
50	187.2±8.0	185.1±10.6	181.4±12.5	171.7±9.3** (↓8)
57	209.7±11.3	205.5±12.5	202.3±13.4	191.6±8.5** (↓9)
63	218.5±12.2	213.2±12.8	208.8±15.1* (↓4)	197.5±11.6** (↓10)

a Data (n=24-29) were obtained from pages 125-128 in MRID 46727403. Statistical analysis was performed by the reviewers (ANOVA followed by Dunnett's test). Percent difference from control (calculated by reviewers) is presented parenthetically.

* Statistically different from control, p≤0.05

** Statistically different from control, p≤0.01

3. Developmental landmarks

a. Sexual maturation: The age when vaginal opening occurred was increased (p≤0.01) at 0.20 (37.4 days) and 0.40 (38.3 days) mg/kg/day compared to controls (35.5 days; Table 7). Although the body weights at landmark were similar to controls in Table 7, examination of the body weight data in Table 6 revealed a 5-10% decrease (p≤0.01) in body weights at approximately the time of vaginal opening (PND 36). Therefore, the delay in vaginal opening was considered to be a result of delayed development associated with decreased growth. No effect of treatment was observed on the time to preputial separation.

TABLE 7. Mean (±SD) age of sexual maturation (days) [a]				
Parameter	Dose (mg/kg/day)			
	Control	0.12	0.20	0.40
N (M/F)	24/24	24/24	29/29	27/27
Preputial separation (males)	44.0±1.3	43.4±1.4	43.9±1.3	44.3±1.7
Vaginal opening (females)	35.5±1.7	36.5±2.3	37.4±2.7**	38.3±2.6**
BW in males at landmark (g)	210±12	204±14	208±11	200±11** (↓5)
BW in females at landmark (g)	125±12	128±12	129±11	127±11

a Data were obtained from pages 129-130 in MRID 46727403. Percent difference from control (calculated by reviewers) is presented parenthetically.

** Statistically different from control, p≤0.01

b. Physical landmarks: Evaluation of physical landmarks was not performed.

4. Behavioral assessments

a. Functional observational battery: No treatment-related effects were observed during the functional observational battery.

b. Motor activity: No treatment-related effects were observed on total motor activity (Table 8). Habituation was unaffected by treatment. Motor activity at PND 18 was usually less than motor activity at PND 14; motor activity was greater at PND 22 than at PND 14 and further increased at PND 60. Habituation was not demonstrated in the 0.40 mg/kg/day males at PND 22, but this isolated occurrence was considered incidental. Subsession motor activity is included in Appendix 3. Differences ($p \leq 0.05$) from controls were sporadic and unrelated to treatment.

TABLE 8a. Mean (±S.D.) motor activity data (total activity counts for session) [a]

Test Day	Dose (mg/kg/day)			
	Control	0.12	0.20	0.40
Males				
PND 14	232±127	234±128	176±82	193±104
PND 18	168±157	163±211	114±106	124±144
PND 22	322±179	319±203	303±172	311±150
PND 60	487±150	463±180	494±164	474±116
Females				
PND 14	167±106	202±134	174±131	151±103
PND 18	161±93	152±142	105±117	155±144
PND 22	332±156	291±162	353±109	324±155
PND 60	564±108	517±117	604±129	571±44

a Data (n=12-15) were obtained from pages 131-138 in MRID 46727403.

TABLE 8b. Mean (±S.D.) sub-session motor activity data in males (# movements/5 minute sub-session) [a]				
Interval (minutes)	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
PND 14				
1-5	41.3±27.4	46.2±28.6	37.9±26.2	37.7±24.0
6-10	23.8±16.4	32.6±25.2	14.9±16.0	32.9±21.9
11-15	23.2±18.5	37.7±25.2	29.7±20.1	29.2±20.4
16-20	29.0±19.6	37.7±29.0	18.8±23.3	26.8±18.5
21-25	16.9±15.5	19.5±18.0	10.6±15.8	23.3±18.8
26-30	24.8±26.6	21.9±24.6	16.6±21.8	14.1±15.9
31-35	24.5±25.5	19.1±23.0	11.9±11.8	5.3±9.2** (↓78)
36-40	17.7±18.8	9.3±14.7	16.9±23.0	6.7±11.9
41-45	9.6±11.7	5.0±7.0	8.9±15.7	9.2±12.7
46-50	20.7±18.4	5.1±7.7* (↓75)	9.6±18.5	7.7±13.3* (↓63)
PND 22				
1-5	28.1±24.6	26.1±30.8	22.9±19.5	17.6±20.2
6-10	23.3±22.4	23.9±36.6	15.4±19.0	17.4±25.3
11-15	21.9±16.9	18.1±25.0	15.4±16.8	19.7±24.9
16-20	15.4±19.6	14.5±27.6	12.4±20.5	14.8±22.3
21-25	14.2±19.8	11.8±30.6	11.9±16.5	16.4±27.2
26-30	18.3±22.4	11.7±27.3	12.6±18.0	8.8±18.0
31-35	10.6±15.5	20.6±31.9	8.4±14.5	5.9±11.0
36-40	13.1±19.1	10.9±13.5	5.1±14.5	6.1±13.5
41-45	10.0±18.7	10.3±16.4	5.8±11.8	7.5±14.6
46-50	13.2±20.4	14.9±22.2	3.8±8.6	9.9±15.0
PND 22				
1-5	41.3±18.6	44.9±26.0	36.6±21.1	33.9±22.7
6-10	33.1±21.7	47.8±32.6	30.2±21.9	26.1±22.7
11-15	28.3±20.1	29.7±29.6	27.3±21.8	26.8±22.5
16-20	31.4±22.0	29.5±20.2	19.7±23.3	30.3±25.4
21-25	26.8±27.7	29.4±18.9	25.7±27.2	28.6±22.7
26-30	37.6±27.0	27.1±26.7	33.9±27.2	39.8±24.3
31-35	33.6±24.0	26.7±23.3	39.4±23.0	38.9±18.5
36-40	33.5±22.4	26.5±24.3	28.6±25.5	31.1±25.1
41-45	30.8±25.7	25.8±19.4	32.4±22.0	20.6±22.9
46-50	25.7±16.8	31.8±26.8	29.6±26.5	34.9±26.4
PND 60				
1-5	62.7±11.0	67.1±7.7	65.6±9.5	61.8±10.0
6-10	63.1±12.1	68.8±11.2	65.0±4.5	64.7±10.2
11-15	54.3±11.1	59.9±15.5	58.3±15.0	55.8±21.4
16-20	43.4±27.2	44.6±23.8	51.3±18.5	53.3±13.4
21-25	37.4±25.7	33.8±27.1	47.4±22.0	44.5±19.6
26-30	33.2±23.6	49.3±22.6	44.3±22.3	31.0±24.1
31-35	43.4±30.5	36.1±32.2	48.6±25.5	36.5±28.3
36-40	46.9±21.4	32.4±31.4	42.1±31.4	37.1±24.9
41-45	54.4±21.1	37.9±32.8	37.6±30.3	45.2±20.6
46-50	48.2±21.2	32.7±31.7	34.1±29.3	44.5±23.1

a Data were obtained from Tables 22-25 on pages 127-134 of the study report. Percent differences from controls (calculated by reviewers) are presented in parentheses.

* Significantly different from control, $p \leq 0.05$

TABLE 8c. Mean (±S.D.) sub-session motor activity data in females (# movements/5 minute sub-session) [a]

Interval (minutes)	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
PND 14				
1-5	49.7±31.7	51.4±29.6	37.6±25.5	39.0±28.3
6-10	28.2±22.5	34.2±28.9	21.5±19.3	23.7±28.4
11-15	17.8±17.7	31.1±28.7	21.7±21.7	20.5±13.8
16-20	22.9±24.6	19.0±24.9	17.9±18.1	21.0±21.9
21-25	13.8±19.9	20.4±28.8	19.6±23.5	8.4±9.9
26-30	10.3±14.7	8.4±10.4	10.3±17.5	4.5±10.1
31-35	8.9±12.0	14.8±21.5	10.9±16.6	10.4±13.4
36-40	4.9±6.9	9.3±11.8	9.9±14.7	12.8±16.1
41-45	7.3±18.3	7.3±13.4	14.3±18.6	6.4±10.2
46-50	2.8±5.4	6.2±6.9	10.7±19.2	4.2±8.5
PND 22				
1-5	23.9±16.6	22.1±26.0	25.3±20.1	22.7±19.2
6-10	28.9±14.0	24.6±24.1	16.0±20.9	18.2±20.4
11-15	23.9±18.9	20.8±27.3	9.0±14.2	13.2±18.0
16-20	15.1±17.8	15.6±20.7	11.2±19.9	18.8±21.6
21-25	11.8±14.3	15.7±17.6	11.7±18.6	11.8±18.7
26-30	17.6±20.2	11.6±18.2	5.8±12.5	16.6±19.5
31-35	13.9±16.7	9.9±15.4	7.2±16.0	13.7±19.1
36-40	2.7±4.2	8.3±10.4	5.5±13.2	13.4±17.9* (↑396)
41-45	13.1±23.3	11.6±16.7	3.9±8.5	12.3±17.7
46-50	9.9±18.9	12.0±21.1	9.3±19.3	13.8±24.2
PND 22				
1-5	415.±18.8	36.2±22.9	42.3±20.1	40.1±20.4
6-10	38.9±24.6	38.8±26.5	35.9±22.0	39.5±22.8
11-15	29.5±19.8	36.8±28.5	27.7±22.5	34.5±23.8
16-20	32.0±20.1	27.4±25.4	28.4±20.5	29.4±27.0
21-25	36.0±23.6	31.4±23.9	31.2±18.6	29.0±21.6
26-30	28.6±19.7	29.4±19.9	37.0±14.9	34.9±27.1
31-35	38.1±22.0	20.6±13.6* (↓46)	38.3±22.6	35.3±23.8
36-40	31.7±22.9	16.8±12.0	36.9±16.9	22.5±24.5
41-45	26.5±22.5	28.0±20.2	36.3±15.7	32.2±25.8
46-50	29.8±17.7	25.8±27.1	38.8±21.0	27.3±25.3
PND 60				
1-5	59.0±11.8	60.8±6.8	64.5±11.6	62.2±6.2
6-10	60.1±9.9	55.5±9.6	68.0±9.6	61.9±9.4
11-15	61.5±11.6	61.9±12.1	66.8±10.6	59.6±10.9
16-20	59.0±22.2	50.5±20.9	58.2±17.7	64.1±7.6
21-25	46.6±22.1	53.2±19.3	52.8±16.8	56.5±8.0
26-30	51.2±25.6	46.6±24.8	55.6±22.1	51.1±12.7
31-35	54.7±15.0	45.7±25.4	57.4±24.9	51.8±13.9
36-40	53.9±18.3	48.2±19.6	61.7±23.7	47.0±14.3
41-45	59.3±13.7	50.9±24.0	59.8±17.5	61.8±8.5
46-50	58.2±16.0	43.9±25.4	59.2±18.5	55.2±9.6

a Data were obtained from Tables 22-25 on pages 127-134 of the study report. Percent differences from controls (calculated by reviewers) are presented in parentheses.

* Significantly different from control, p≤0.05

** Significantly different from control, p≤0.01

c. **Auditory startle reflex habituation:** No treatment-related effects were observed on the auditory startle reflex (Tables 9a and 9b). Peak amplitude was decreased ($p \leq 0.05$) by 26% in the 0.40 mg/kg/day females at PND 61 during Block 1; this isolated decrease was considered incidental. Other differences ($p \leq 0.05$) in peak amplitude or latency on PND 23 or 61 were minor and/or unrelated to dose.

TABLE 9a. Mean (±SD) interval acoustic startle peak amplitude (g) and latency to peak (ms) in F1 male rats[a]

Dose (mg/kg/day)	Parameter	Block 1	Block 2	Block 3	Block 4	Block 5
PND 23						
Control	Peak Amp.	408±246	238±72	203±93	180±80	207±71
	Latency	27.9±6.3	21.6±2.2	21.7±2.6	21.0±1.5	21.1±1.8
0.12	Peak Amp.	446±257	380±362	294±230	241±146	220±108
	Latency	28.6±7.7	22.5±7.2	22.6±6.4	22.0±3.5	21.1±2.8
0.20	Peak Amp.	546±351	321±116	277±119	230±91	238±87
	Latency	28.8±6.7	22.7±5.0	22.1±3.5	21.4±2.0	21.3±3.2
0.40	Peak Amp.	548±226	381±205	328±169	245±133	268±134
	Latency	28.9±6.5	23.6±5.3	22.4±5.1	22.4±4.3	22.8±5.8
PND 61						
Control	Peak Amp.	1542±741	961±507	817±484	734±456	805±479
	Latency	29.0±6.9	23.8±2.8	26.5±5.2	24.9±3.1	25.6±3.3
0.12	Peak Amp.	1447±433	1081±498	1071±492	916±358	1094±668
	Latency	26.4±4.1	25.3±2.6	25.3±2.3	24.7±1.8	25.8±4.7
0.20	Peak Amp.	1749±515	1152±557	1135±545	1152±524* (↑57)	1005±531
	Latency	29.1±8.0	23.6±2.3	23.6±3.0* (↓11)	23.7±3.5	24.4±3.8
0.40	Peak Amp.	1485±429	1132±293	1090±367	1074±316	895±260
	Latency	25.7±5.5	23.7±2.6	23.6±2.7* (↓11)	23.5±2.3	25.4±4.1

a Data (n=11-15) were obtained on pages 139-146 of MRID 46727403; 10 trials/block. Percent difference from controls (calculated by reviewers) is presented parenthetically.

* Statistically different from controls at $p \leq 0.05$

TABLE 9b. Mean (±SD) interval acoustic startle peak amplitude (g) and latency to peak (ms) in F1 female rats[a]						
Dose (mg/kg/day)	Parameter	Block 1	Block 2	Block 3	Block 4	Block 5
PND 23						
Control	Peak Amp.	493±245	364±268	380±321	258±143	240±96
	Latency	32.9±11.1	26.6±9.6	25.7±8.7	23.4±6.4	22.7±6.9
0.12	Peak Amp.	754±363* (↑53)	461±350	396±303	382±276	320±229
	Latency	30.6±6.5	23.7±6.6	23.2±6.3	21.9±6.2	24.2±6.4
0.20	Peak Amp.	565±277	434±309	326±196	244±84	214±86
	Latency	30.6±8.4	24.5±7.2	23.3±3.6	21.3±1.7	21.6±2.9
0.40	Peak Amp.	574±244	348±107	320±127	275±86	249±100
	Latency	29.3±8.2	21.7±4.3	22.3±4.3	21.3±3.6	21.0±3.0
PND 61						
Control	Peak Amp.	1403±329	1136±421	906±366	779±269	834±273
	Latency	25.2±3.2	23.7±4.0	24.1±3.0	25.8±4.2	26.2±2.1
0.12	Peak Amp.	1204±338	989±320	879±394	709±416	724±403
	Latency	25.5±4.4	23.2±2.1	23.8±2.8	24.5±1.9	25.0±2.8
0.20	Peak Amp.	1222±384	1025±414	879±418	1008±406	860±322
	Latency	23.7±2.7	23.8±3.2	23.1±2.7	23.0±2.2* (↓11)	22.8±1.4** (↓13)
0.40	Peak Amp.	1035±375* (↓26)	931±297	946±388	777±374	747±324
	Latency	25.5±3.7	23.6±3.3	23.9±1.2	26.3±3.9	26.4±3.7

a Data (n=11-14) were obtained on pages 139-146 of MRID 46727403; 10 trials/block. Percent difference from controls (calculated by reviewers) is presented parenthetically.

* Statistically different from control, $p \leq 0.05$

** Statistically different from control, $p \leq 0.01$

d. Learning and memory testing: No treatment-related differences in learning or memory were noted in any treated group relative to concurrent controls in the water maze tests (Tables 10a and 10b). Learning was demonstrated based on the decreased time to complete the maze on trial 6 vs trial 1 in the learning phase. Less than half (or approximately half) the time was required for maze completion on trial 6 compared to trial 1. Memory was demonstrated in that the first trial in the memory phase was completed in approximately a half to a third of the time required for the first trial in the learning phase. Differences ($p \leq 0.05$) were sporadic, unrelated to dose, and/or improvements over the control. The proportion of successful trials was calculated as the number of trials completed in less than 3, 4, 5, 6, 7, 8, 9, or 10 seconds or less than 1.0x, 1.5x, or 2.0x the time required to complete the straight channel (Tables 11a and 11b). The differences ($p \leq 0.05$) in the proportion of successful trials were either increases in successes over the controls or were not dose-related.

TABLE 10a. Water Maze Performance (s) in Offspring (mean±S.D.) [a]

Session/Parameter		Dose (mg/kg/day)			
		Control	0.12	0.20	0.40
Males					
Learning Phase, PND 24	Straight channel	2.82±0.88	3.20±1.51	3.37±1.54	3.28±1.71
	Latency trial 1	13.93±6.97	13.14±6.58	13.54±6.73	11.65±5.84
	Latency trial 2	9.30±6.83	6.76±4.45	7.27±5.97	7.72±3.79
	Latency trial 3	7.78±3.37	4.99±2.89	6.82±6.52	5.83±5.82
	Latency trial 4	5.09±3.24	5.13±3.67	5.71±4.95	5.02±3.28
	Latency trial 5	5.47±3.31	4.06±1.95	5.01±3.30	4.13±2.50
	Latency trial 6	5.55±5.44	4.69±2.80	4.93±2.67	6.08±4.31
Memory Phase, PND 27	Straight channel	3.99±3.25	3.83±2.12	3.80±2.40	3.71±2.33
	Latency trial 1	6.85±4.22	5.25±2.24	6.10±3.26	6.10±2.87
	Latency trial 2	4.07±3.02	4.33±4.25	4.24±2.76	4.33±3.48
	Latency trial 3	4.91±4.05	5.39±3.68	5.02±5.21	3.56±1.52
	Latency trial 4	5.34±6.14	4.32±1.98	5.25±3.51	5.08±3.47
	Latency trial 5	6.39±6.30	6.93±7.29	6.75±4.04	4.79±3.75
	Latency trial 6	5.77±3.66	5.43±3.84	6.21±4.17	6.20±4.64
Females					
Learning Phase, PND 24	Straight channel	3.35±1.79	3.19±1.06	3.62±1.55	2.84±1.17
	Latency trial 1	14.64±5.49	13.01±5.74	13.13±7.12	12.37±8.79
	Latency trial 2	6.81±4.85	9.45±7.30	6.75±2.92	7.43±4.82
	Latency trial 3	7.83±6.48	6.30±4.48	6.49±4.32	8.41±6.14
	Latency trial 4	5.33±3.55	5.95±4.75	6.77±4.43	4.89±3.03
	Latency trial 5	6.95±5.91	5.73±4.57	5.99±4.49	5.18±4.45
	Latency trial 6	6.30±5.16	6.68±6.17	5.51±5.18	5.24±4.33
Memory Phase, PND 27	Straight channel	3.60±2.56	3.19±1.77	3.43±1.98	3.07±1.82
	Latency trial 1	8.00±3.94	8.77±5.14	8.45±4.57	7.46±3.72
	Latency trial 2	4.96±3.85	3.15±1.30* (↓36)	4.63±3.07	4.92±2.86
	Latency trial 3	5.04±2.62	3.88±2.36	4.21±3.24	3.49±1.66* (↓31)
	Latency trial 4	5.34±4.11	4.38±3.06	4.98±3.26	3.88±3.26
	Latency trial 5	4.89±3.92	5.54±4.09	4.10±2.48	4.24±3.44
	Latency trial 6	4.49±3.63	6.38±6.08	5.15±4.27	4.57±3.47

a Data (n=24-29) were obtained from pages 147-150 in MRID 46727403. Percent difference from controls (calculated by reviewers) is presented parenthetically.

* Statistically different from control, $p<0.05$

TABLE 10b. Water Maze Performance (s) in Offspring (mean±S.D.) [a]

Session/Parameter		Dose (mg/kg/day)			
		Control	0.12	0.20	0.40
Males					
Learning Phase, PND 59	Straight channel	2.79±1.01	2.47±0.46	2.88±1.09	2.59±0.58
	Latency trial 1	9.49±5.36	9.54±3.61	10.30±3.11	9.02±4.06
	Latency trial 2	6.17±5.10	3.98±1.71* (↓35)	5.10±2.94	4.99±2.41
	Latency trial 3	4.32±3.10	3.48±1.35	4.54±2.59	4.18±2.37
	Latency trial 4	3.28±1.10	4.93±3.98* (↑50)	3.83±1.91	4.10±1.96
	Latency trial 5	3.75±2.52	3.95±3.05	4.03±2.21	4.70±4.05
	Latency trial 6	3.69±2.33	3.39±1.65	3.47±1.06	3.71±2.68
Memory Phase, PND 62	Straight channel	2.87±1.25	2.43±0.45	2.38±0.46* (↓17)	2.64±0.91
	Latency trial 1	4.94±2.37	5.67±4.06	6.09±3.56	5.39±4.32
	Latency trial 2	5.85±4.17	5.19±3.40	4.80±3.31	5.20±3.48
	Latency trial 3	7.82±6.23	5.57±3.82	5.93±4.84	5.95±5.30
	Latency trial 4	7.18±6.63	6.18±5.01	5.92±2.85	5.40±4.28
	Latency trial 5	8.79±6.61	5.84±4.34* (↓34)	6.63±4.48	5.04±4.24** (↓43)
	Latency trial 6	8.22±6.24	6.03±4.47	6.04±4.22	4.86±4.34* (↓41)
Females					
Learning Phase, PND 59	Straight channel	2.93±1.31	2.60±0.99	3.27±1.63	3.04±1.60
	Latency trial 1	11.88±4.62	9.99±4.82	10.84±3.58	12.88±5.37
	Latency trial 2	5.56±3.37	4.76±2.52	6.10±3.81	5.55±3.72
	Latency trial 3	6.05±5.03	4.46±3.03	4.83±2.78	4.40±2.34
	Latency trial 4	4.08±2.87	5.26±6.01	4.73±3.27	3.98±2.18
	Latency trial 5	4.32±3.26	3.94±2.50	4.24±3.78	3.29±1.66
	Latency trial 6	3.65±2.14	4.89±4.62	5.58±3.13	4.46±4.02
Memory Phase, PND 62	Straight channel	2.79±1.42	2.52±0.77	2.71±0.74	2.70±0.83
	Latency trial 1	4.77±2.26	5.46±3.24	5.88±2.88	6.00±2.47
	Latency trial 2	5.80±5.76	4.93±3.78	5.40±4.16	5.49±5.42
	Latency trial 3	6.11±4.54	5.66±4.71	5.83±5.67	6.44±6.46
	Latency trial 4	5.15±3.05	6.52±4.27	6.96±5.66	9.54±7.39** (↑85)
	Latency trial 5	8.16±6.70	9.15±6.52	10.41±8.14	7.18±5.92
	Latency trial 6	8.95±6.81	6.50±4.51	7.66±6.15	6.42±5.23

a Data (n=22-28) were obtained from pages 151-154 in MRID 46727403. Percent difference from controls (calculated by reviewers) is presented parenthetically.

* Statistically different from control, $p<0.05$

** Statistically different from control, $p<0.01$

TABLE 11a. Water maze performance: Mean (±SD) proportion of successful trials on PND 24 and 27 [a]

Session/Parameter		Dose (mg/kg/day) 0	0.12	0.20	0.40
Males					
Learning Phase, PND 24	Cut-off 3 sec	20.1±22.0	23.6±24.5	24.7±23.0	23.5±20.8
	Cut-off 4 sec	35.4±23.7	47.9±24.2	44.3±27.6	40.7±23.7
	Cut-off 5 sec	40.3±23.0	55.6±22.3* (↑38)	54.0±23.4* (↑34)	51.9±20.8
	Cut-off 6 sec	49.3±24.3	62.5±21.0* (↑27)	59.2±25.0	61.1±21.7
	Cut-off 7 sec	59.0±22.5	68.8±18.6	65.5±25.6	64.8±21.4
	Cut-off 8 sec	63.9±20.1	77.8±12.7* (↑22)	70.7±21.2	70.4±21.8
	Cut-off 9 sec	68.8±20.4	79.9±13.0* (↑16)	74.1±18.1	77.2±21.8* (↑12)
	Cut-off 10 sec	76.4±12.9	81.3±12.3	75.9±18.7	80.9±20.0
	Cut-off 1.0x straight channel	10.4±20.2	21.5±30.5	25.9±28.7* (↑149)	17.9±29.6
	Cut-off 1.5x straight channel	34.0±24.3	47.9±27.9	48.3±28.3	47.5±31.6
	Cut-off 2.0x straight channel	47.9±21.6	61.8±21.1	58.6±25.0	58.0±27.1
Memory Phase, PND 27	Cut-off 3 sec	43.1±25.0	34.7±22.5	31.0±22.6	37.0±25.0
	Cut-off 4 sec	60.4±23.5	49.3±23.8	50.0±23.6	53.1±22.2
	Cut-off 5 sec	64.6±23.7	61.8±21.1	59.2±19.7	66.0±18.2
	Cut-off 6 sec	70.1±25.5	72.2±14.5	66.7±19.9	74.7±16.3
	Cut-off 7 sec	75.0±23.1	82.6±15.9	73.6±21.6	80.2±15.4
	Cut-off 8 sec	77.8±22.3	87.5±12.3	78.2±18.4	84.6±14.6
	Cut-off 9 sec	80.6±20.7	89.6±12.8	83.9±16.4	89.5±14.0* (↑11)
	Cut-off 10 sec	86.1±17.5	91.0±11.0	87.4±15.2	91.4±12.5
	Cut-off 1.0x straight channel	29.9±35.4	38.9±27.7	28.7±32.1	34.0±32.8
	Cut-off 1.5x straight channel	63.2±29.9	65.3±25.5	57.5±26.2	63.0±23.3
	Cut-off 2.0x straight channel	72.2±2.59	75.0±19.7	71.8±22.3	77.2±19.1
Females					
Learning Phase, PND 24	Cut-off 3 sec	22.9±24.5	22.2±19.5	13.2±20.1	25.3±24.6
	Cut-off 4 sec	42.4±25.5	41.0±21.4	34.5±20.4	44.4±27.0
	Cut-off 5 sec	47.9±22.7	47.9±22.2	46.0±18.2	52.5±24.3
	Cut-off 6 sec	52.8±23.4	52.1±22.2	52.3±21.7	58.0±23.7
	Cut-off 7 sec	56.3±21.3	58.3±23.6	60.9±21.0	63.0±23.7
	Cut-off 8 sec	59.7±20.2	64.6±22.7	66.1±20.2	67.3±22.9
	Cut-off 9 sec	64.6±19.2	64.6±22.7	72.4±16.8	72.2±20.7
	Cut-off 10 sec	66.7±19.7	68.8±20.4	75.9±16.4	75.3±20.3
	Cut-off 1.0x straight channel	13.2±19.6	18.8±20.4	25.3±29.4	18.5±22.8
	Cut-off 1.5x straight channel	47.2±26.3	44.4±24.9	43.7±26.5	42.6±27.9
	Cut-off 2.0x straight channel	55.6±23.9	53.5±24.6	58.0±23.8	56.8±24.1
Memory Phase, PND 27	Cut-off 3 sec	33.3±22.5	43.1±24.0	37.9±22.7	46.3±23.3
	Cut-off 4 sec	52.8±23.9	56.9±21.9	52.3±23.5	63.0±20.8
	Cut-off 5 sec	61.8±24.8	61.8±21.7	66.1±17.0	69.8±18.5
	Cut-off 6 sec	71.5±21.1	66.7±20.9	72.4±15.0	74.1±17.5
	Cut-off 7 sec	76.4±21.9	77.1±18.9	78.7±14.7	79.6±14.9
	Cut-off 8 sec	79.9±20.8	80.6±17.5	83.9±12.2	84.0±9.8
	Cut-off 9 sec	84.7±20.2	83.3±15.5	85.6±13.2	86.4±10.4
	Cut-off 10 sec	86.8±16.3	87.5±15.7	87.9±12.5	89.5±11.5
	Cut-off 1.0x straight channel	34.7±28.6	25.0±29.1	25.9±29.4	26.5±30.0
	Cut-off 1.5x straight channel	59.7±26.4	57.6±26.9	59.8±22.9	56.8±25.0
	Cut-off 2.0x straight channel	68.8±25.2	66.0±25.8	73.6±20.7	71.0±16.4

a Data were obtained from Table 29 on pages 151-165of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.

* Statistically different from control, $p \leq 0.05$

TABLE 11b. Water maze performance: Mean (±SD) proportion of successful trials on PND 59 and 62 [a]

Session/Parameter		Dose (mg/kg/day) 0	0.12	0.20	0.40
Males					
Learning Phase, PND 59	Cut-off 3 sec	33.3±26.9	36.8±26.5	28.6±24.8	35.9±24.4
	Cut-off 4 sec	59.7±19.0	59.0±24.6	58.3±17.3	51.3±23.1
	Cut-off 5 sec	67.4±13.4	69.4±16.8	63.1±15.3	64.1±20.4
	Cut-off 6 sec	74.3±9.8	76.4±14.7	69.6±15.7	705±18.4
	Cut-off 7 sec	79.2±13.2	81.3±13.3	75.6±16.0	80.8±18.7
	Cut-off 8 sec	82.6±11.5	84.7±14.7	79.2±14.1	84.6±16.9
	Cut-off 9 sec	88.2±11.5	87.5±14.1	83.9±13.2	88.5±14.0
	Cut-off 10 sec	91.0±9.8	89.6±12.8	89.3±12.2	90.4±12.6
	Cut-off 1.0x straight channel	20.1±27.4	15.3±20.2	19.6±30.4	19.2±22.5
	Cut-off 1.5x straight channel	56.3±21.9	53.5±26.5	52.4±27.5	51.9±23.7
	Cut-off 2.0x straight channel	69.4±16.8	67.4±17.4	65.5±19.2	60.3±23.1
Memory Phase, PND 62	Cut-off 3 sec	23.6±25.5	34.0±27.1	20.8±24.3	34.6±26.2
	Cut-off 4 sec	38.9±25.9	52.8±27.2	40.5±27.8	56.4±27.9* (↑45)
	Cut-off 5 sec	49.3±28.4	56.9±24.5	49.4±27.4	67.3±25.6* (↑37)
	Cut-off 6 sec	54.9±28.0	66.7±24.6	63.1±25.4	74.4±24.1* (↑36)
	Cut-off 7 sec	62.5±27.5	73.6±21.4	72.6±21.9	78.8±22.9* (↑26)
	Cut-off 8 sec	68.8±27.5	77.8±22.3	77.4±21.4	86.5±18.9** (↑26)
	Cut-off 9 sec	73.6±25.0	80.6±21.8	83.9±15.4	87.2±19.0* (↑18)
	Cut-off 10 sec	79.2±22.1	82.6±20.0	89.3±13.0	89.1±16.3
	Cut-off 1.0x straight channel	14.6±25.2	14.6±19.2	6.0±15.9	17.3±25.2
	Cut-off 1.5x straight channel	41.0±31.8	44.4±24.9	32.7±27.8	51.3±32.6
	Cut-off 2.0x straight channel	53.5±29.9	56.3±24.5	48.2±28.5	64.7±26.0
Females					
Learning Phase, PND 59	Cut-off 3 sec	31.8±23.5	37.7±25.2	20.7±20.6	32.7±26.9
	Cut-off 4 sec	53.0±20.3	51.4±23.5	44.0±22.5	55.8±26.2
	Cut-off 5 sec	61.4±118.1	59.4±20.6	56.7±15.2	60.9±25.8
	Cut-off 6 sec	65.9±17.4	69.6±17.9	63.3±13.6	66.7±18.9
	Cut-off 7 sec	68.9±17.3	74.6±16.6	68.7±13.0	73.1±17.7
	Cut-off 8 sec	73.5±16.0	77.5±17.8	73.3±13.6	76.9±16.4
	Cut-off 9 sec	78.0±14.9	84.8±15.0	79.3±12.1	78.8±14.6
	Cut-off 10 sec	84.1±10.9	89.9±10.9	84.0±12.2	84.0±10.0
	Cut-off 1.0x straight channel	22.0±26.4	19.6±25.5	24.0±28.5	24.4±28.4
	Cut-off 1.5x straight channel	49.2±22.7	52.2±26.7	48.7±26.8	52.6±23.9
	Cut-off 2.0x straight channel	62.1±18.7	58.7±26.0	64.7±21.1	67.3±19.7
Memory Phase, PND 62	Cut-off 3 sec	31.1±25.9	32.6±30.8	18.7±20.6	31.4±26.4
	Cut-off 4 sec	445.5±21.9	41.3±29.7	37.3±23.2	44.2±22.6
	Cut-off 5 sec	55.3±20.8	52.2±23.2	52.7±20.2	55.8±23.5
	Cut-off 6 sec	62.1±20.7	61.6±23.3	63.3±22.6	60.9±23.1
	Cut-off 7 sec	67.4±18.2	66.7±20.7	71.3±21.8	66.0±25.6
	Cut-off 8 sec	72.0±14.0	71.0±20.9	74.0±19.9	71.8±25.3
	Cut-off 9 sec	78.0±15.8	73.2±21.8	80.0±18.0	78.2±22.0
	Cut-off 10 sec	83.3±13.6	76.8±18.6	81.3±17.6	81.4±21.3
	Cut-off 1.0x straight channel	10.6±20.3	15.2±21.9	10.7±20.9	12.8±20.2
	Cut-off 1.5x straight channel	49.2±22.7	43.5±27.4	38.7±28.3	44.2±26.6
	Cut-off 2.0x straight channel	59.8±24.5	55.1±26.8	54.7±25.2	54.5±26.9

a Data were obtained from Table 29 on pages 15-165of the study report. Percent difference from controls (calculated by reviewers) is presented parenthetically.

* Statistically different from control, $p \leq 0.05$

** Statistically different from control; p≤0.01

5. Postmortem results

a. **Brain weights:** No effects of treatment were observed on brain weights of offspring on PND 12 or 63 (Table 12). A minor decrease (p≤0.05) of 3% was noted in the brain weight in 0.40 mg/kg/day females on PND 63 prior to fixation. Other differences (p≤0.05) were unrelated to dose (see Appendix 5 to this DER).

TABLE 12. Mean (±SD) brain weight data [a]

Parameter	Dose (mg/kg/day)			
	0	0.12	0.20	0.40
Males				
Day 12				
Brain weight (g)	1.09±0.04	1.15±0.07** (↑6)	1.15±0.04** (↑6)	1.12±0.03
PND 63 (non-perfused)				
Brain weight (g)	1.98±0.07	1.98±0.08	1.94±0.05	1.95±0.06
PND 63 (perfused)				
Brain weight (g)	2.05±0.12	2.04±0.14	2.06±0.08	1.98±0.08
Females				
Day 12				
Brain weight (g)	1.09±0.07	1.12±0.04	1.08±0.04	1.09±0.06
PND 63 (non-perfused)				
Brain weight (g)	1.83±0.04	1.81±0.07	1.84±0.03	1.78±0.05* (↓3)
PND 63 (perfused)				
Brain weight (g)	1.92±0.08	1.93±0.07	1.88±0.09	1.92±0.06

a Data (n=12-15) were obtained from pages 171-172 of MRID 46727403. Percent difference from controls (calculated by reviewers) is presented parenthetically.
* Statistically different from control, p<0.05
** Statistically different from control, p<0.01

b. Neuropathology

1. **Macroscopic examination:** No treatment-related gross pathological findings were noted.

2 **Microscopic examination:** No treatment-related histopathological findings were observed. Demyelination in the distal tibial nerve (6 treated vs 3 control females) and proximal tibial nerve (7 treated vs 4 control males) were noted (n=10), but not considered adverse due to minimal severity.

Brain morphometry data were not included in the study report, due to procedural deficiencies that rendered the data uninterpretable.

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** The investigators concluded that there was no evidence of developmental neurotoxicity at doses up to 0.40 mg/kg/day. All dose levels were associated with higher maternal body weight and food consumption during the dosing period. The 0.20 and 0.40 mg/kg/day F1 groups had decreased bodyweights post-weaning and hence a slight delay in the time of vaginal opening. No effect on the function or morphology of the nervous system was observed.

B. **REVIEWER'S COMMENTS**

1. **Maternal toxicity:** There were no effects of treatment on mortality, clinical signs, functional observational battery parameters, body weights, body weight gains, food consumption, reproductive performance, or gestation length.

   One control female and one 0.4 mg/kg/day female were killed on GD 25, because they failed to litter. Both females were found not to have been pregnant at necropsy. One 0.12 mg/kg/day female was killed after a total litter loss. Dams (1-5/group, unrelated to dose) were killed because they produced an insufficient number of pups (<3 males and 3 females in a litter or <7 pups).

   The maternal LOAEL was not observed. The maternal NOAEL is 0.4 mg/kg/day.

2. **Offspring toxicity:** No treatment-related effects were observed on litter parameters (number born live, number born dead, sex ratio (% male), mean litter size, live birth index, and viability index), clinical signs, FOB parameters, motor activity, auditory startle reflex, learning and memory, sexual maturation, brain weight, or gross or microscopic pathology.

   On the day of weaning (PND 29), minor decreases ($p \leq 0.05$) in pup body weights were observed at 0.40 mg/kg/day (↓5-7%). Pup body weights continued to be decreased ($p \leq 0.01$) by 5-6% in the males and by 8-10% in the females throughout the post-weaning interval (PND 36-63).

   The offspring LOAEL is 0.4 mg/kg/day, due to decreased body weights in both sexes. The NOAEL is 0.2 mg/kg/day.

   There was no evidence of neurotoxicity in the offspring.
   This study is classified as acceptable/non-guideline. The results of this study should be considered together with those of a follow-up study conducted in 2007 (MRID 47116201).

C. **STUDY DEFICIENCIES:** The following minor deficiencies were noted but do not affect the conclusions of this report:

- Adequate positive control data for neurotoxicity testing were not provided.
- Stability data of the compound in the formulation were not provided.

- In life dates were not reported.
- All necessary details concerning the methodology of the functional observational battery, motor activity, auditory startle reflex, and learning and memory testing were not provided.
- Brain morphometric analysis was done for control and 0.4 mg/kg/day groups terminated at 12 and 63 days of age. However, key procedural deficiencies were identified, which the Sponsor concluded made this data uninterpretable; therefore, these data were not included in the Study Report.

APPENDIX 1

In this rangefinding preliminary developmental neurotoxicity study (MRID 46727402), abamectin (96.2% a.i.; CTL test substance reference no. Y12230/002) was administered to 10 female Wistar-derived (Alpk:AP$_f$SD) rats/dose in the diet at dose levels of 0, 2, 5, 10, or 20 ppm (equivalent to 0.253, 0.604, 0.876, and 1.486 mg/kg/day) from gestation day (GD) 7 through *post partum* day (PND) 23, inclusive. The day of confirmation of mating was designated as GD 1, and the day of littering was designated as PND 1. Clinical signs, body weight, and food consumption during gestation were monitored in the dams. The number of pups and their survival were recorded. Clinical signs and body weights of the pups were monitored.

No adverse effect was observed on maternal body weight, food consumption, or reproductive performance.

At 5 ppm in the pups, decreased (not statistically significant [NS]) total litter weights were observed at PND 15-23 (↓5-23%). Survival was higher at 5 ppm than in the controls throughout the study, and no clinical signs of toxicity were observed. Consequently, the effect on body weights (without statistical significance) is considered equivocal.

At 10 ppm and above in the pups, survival (including whole litter losses) was decreased ($p \leq 0.01$) at PND 12 until termination (0-12.8% treated vs 65.9% controls). Total litter weights were decreased ($p \leq 0.05$) at PND 12 at 10 ppm (↓82%) and at PND 5 and 8 at 20 ppm (↓49-64%). All pups died in these dose groups before other total litter weights were measured.

The LOAEL is 10 ppm (equivalent to 0.876 mg/kg/day), based on decreased survival and body weights in the F1-generation.

This study is classified as **acceptable/non-guideline**.

COMPLIANCE: Signed and dated Data Confidentiality, GLP Compliance, Flagging, and Quality Assurance statements were provided.

APPENDIX 2

In this special study (MRID 46727401), the goal was to generate pharmacokinetics data for [^{14}C] avermectin $B1_a$ in rats (dams and pups) following either gavage or dietary administration to the dams during gestation and lactation. This data would be used to assist the selection of dose levels and to determine the method of administration for the subsequent developmental neurotoxicity study. Avermectin B_{1a} (95.2% radiochemical purity; Batch No. CL-LV-23) was administered to 3 pregnant Wistar-derived (Alpk:AP$_f$SD) rats/dose from gestation day (GD) 7 through *post partum* day (PND) 11 (high dose group only) or PND 18 (other dose groups). Administration occurred through the diet at dose levels of 2, 5, or 10 ppm (equivalent to 0.19, 0.45, and 0.79 mg/kg/day) or by daily gavage doses (in sesame oil vehicle) at dose levels of 0.16, 0.4, or 0.8 mg/kg/day. Thus, the gavage doses were similar to the doses achieved through dietary intake. Clinical observation, body weight, and food consumption measurements were made. Radioassays were performed on samples of milk and pup blood, brain and carcass (collected from 1 male and 1 female) on PND 4, 6, 8, and 11 (high dose) or PND 4, 8, 11, or 18 (other doses). Also, radioassays were performed on samples of dam blood and brain collected on PND 11 (high dose) or 18 (other doses).

Dam body weights were not affected following dietary exposure (data not reported for the groups treated by gavage). Pup body weight gains in respective groups (low, mid, and high) treated by gavage were similar to those treated with diet. A dose-dependent decrease in body weight gain was observed, and the effect at the high dose was severe (↓44-58% at PND 11; Tables 1a and 1b). The gavage-dosed groups were culled to 8 pups on PND 4, and had 0, 5, and 5 unscheduled deaths in the 0.16, 0.4, and 0.8 mg/kg/day groups, respectively. The dietary treated groups were not culled in order to increase the number of pups available for sampling. Thus, comparison of the two exposure routes cannot be done. In the dietary group, 3 unscheduled deaths occurred at 2 and 5 ppm, and 24 deaths were noted at 10 ppm.

No attempt was made to quantitatively account for the administered radioactivity. Although kinetic data generated for the study was based on single time point sampling, data suggest that steady state kinetics had probably been achieved before sampling began.

TABLE 1a. Mean male pup body weight (g) [a]			
Study day	Dose (mg/kg/day) [b]		
	0.16 or 0.19	0.40 or 0.45	0.80 or 0.79
Gavage-treatment			
PND 1	6.62	6.70	5.85
PND 11	23.58	14.80	13.20
PND 18	35.30	26.03	-
BWG (PND 1-11) [c]	16.96	8.1 (↓52)	7.35 (↓57)
Dietary exposure			
PND 1	5.82	5.52	6.32
PND 11	20.42	16.22	8.60
PND 18	39.37	26.03	-
BWG (PND 1-11) [c]	14.6	10.7 (↓27)	2.28 (↓84)

a Data were obtained from page 27 of MRID 46727401.
b Doses listed as concentration in groups treated by gavage or through the diet.
c Body weight gain and percent difference from control were calculated by the reviewers.

TABLE 1b. Mean female pup body weight (g) [a]			
Study day	Dose (mg/kg/day) [b]		
	0.16 or 0.19	0.40 or 0.45	0.80 or 0.79
Gavage-treatment			
PND 1	6.13	6.34	5.52
PND 11	22.80	18.47	10.40
PND 18	37.30	24.00	-
BWG (PND 1-11) [c]	16.67	12.13 (↓27)	4.88 (↓71)
Dietary exposure			
PND 1	5.50	5.31	5.79
PND 11	19.89	16.42	8.45
PND 18	36.25	28.80	-
BWG (PND 1-11) [c]	14.39	11.11 (↓23)	2.66 (↓82)

a Data were obtained from page 27 of MRID 46727401.
b Doses are listed as concentration in groups treated by gavage or through the diet.
c Body weight gain and percent difference from control were calculated by the reviewers.

The route of exposure did not influence the concentration of radioactivity in any sample matrix from either the dam or pup (Tables 2 and 3; from pages 54 and 55 of MRID 46727401). Dose-dependent increases in radioactivity were observed in all sample matrices.

TABLE 2 - MEAN CONCENTRATION OF RADIOACTIVITY IN TISSUES OF ANIMALS FROM THE GAVAGE DOSE GROUPS

Group 4 (0.16 mg/kg)

Tissue	Concentration (µg/g)			
	Day 4-*post partum*	Day 8-*post partum*	Day 11-*post partum*	Day 18-*post partum*
Dam plasma	0.033	0.040	0.030	0.028
Milk	0.083	0.231	0.125	0.097
Pup 1 plasma / Pup 2 plasma	0.050	0.060	0.051	0.050
Pup brain	0.022	0.032	0.029	0.023
Pup carcass	0.112	0.192	0.189	0.194
Dam brain	-	-	-	0.005
Dam carcass	-	-	-	0.309

Group 5 (0.4 mg/kg)

Tissue	Concentration (µg/g)			
	Day 4-*post partum*	Day 8-*post partum*	Day 11-*post partum*	Day 18-*post partum*
Dam plasma	0.088	0.086	0.087	0.087
Milk	0.556	0.514	0.560	0.512
Pup 1 plasma / Pup 2 plasma	0.126	0.187	0.222	0.193
Pup brain	0.080	0.115	0.106	0.085
Pup carcass	0.240	0.438	0.521	0.487
Dam brain	-	-	-	0.015
Dam carcass	-	-	-	0.852

Group 6 (0.8 mg/kg)

Tissue	Concentration (µg/g)			
	Day 4-*post partum*	Day 6-*post partum*	Day 8-*post partum*	Day 11-*post partum*
Dam plasma	0.177	-	0.165	0.155
Milk	0.683	-	0.619	0.709
Pup 1 plasma / Pup 2 plasma	0.228	0.290	0.212	0.274
Pup brain	0.110	0.135	0.124	0.135
Pup carcass	0.481	0.483	0.426	0.474
Dam brain	-	-	-	0.023
Dam carcass	-	-	-	-

TABLE 3 - MEAN CONCENTRATION OF RADIOACTIVITY IN TISSUES OF ANIMALS FROM THE DIET DOSE GROUPS

Group 1 (2ppm)

Tissue	Concentration (µg/g)			
	Day 4-*post partum*	Day 8-*post partum*	Day 11-*post partum*	Day 18-*post partum*
Dam plasma	0.025	0.041	0.029	0.033
Milk	0.085	0.107	0.111	0.183
Pup 1 plasma / Pup 2 plasma	-	0.050	0.052	0.067
Pup brain	0.018	0.031	0.038	0.033
Pup carcass	0.088	0.151	0.204	0.234
Dam brain	-	-	-	0.006
Dam carcass	-	-	-	0.788

Group 2 (5ppm)

Tissue	Concentration (µg/g)			
	Day 4-*post partum*	Day 8-*post partum*	Day 11-*post partum*	Day 18-*post partum*
Dam plasma	0.079	0.084	0.088	0.085
Milk	0.303	0.334	0.464	0.348
Pup 1 plasma / Pup 2 plasma	-	0.136	0.154	0.204
Pup brain	0.055	0.090	0.110	0.093
Pup carcass	0.275	0.390	0.456	0.591
Dam brain	-	-	-	0.013
Dam carcass	-	-	-	0.749

Group 3 (10ppm)

Tissue	Concentration (µg/g)			
	Day 4-*post partum*	Day 6-*post partum*	Day 8-*post partum*	Day 11-*post partum*
Dam plasma	0.109	0.106	0.096	0.067
Milk	0.525	0.463	0.474	-
Pup 1 plasma / Pup 2 plasma	-	0.288	0.317	-
Pup brain	0.104	0.161	0.129	-
Pup carcass	-	-	-	-
Dam brain	-	-	-	-
Dam carcass	-	-	-	0.149

The data also suggests that the compound concentrates in the milk, resulting in the pups being exposed to higher doses than the dams (Tables 4 and 5).

TABLE 4. Mean concentration (µg/g) of radioactivity at PND 8 [a]

Matrix	Dose (mg/kg/day) [b]		
	0.16 or 0.19	0.40 or 0.45	0.80 or 0.79
Gavage-treatment			
Dam plasma	0.040	0.086	0.165
Milk	0.231	0.514	0.619
Pup plasma	0.060	0.187	0.212
Dietary exposure			
Dam plasma	0.041	0.084	0.096
Milk	0.107	0.334	0.474
Pup plasma	0.050	0.136	0.317

a Data were obtained from pages 54 and 55 of MRID 46727401.
b Doses are listed as concentration in groups treated by gavage or through the diet.

TABLE 5. Comparison of distribution of radioactivity into compartments in dam and pup [a]

Dam or pup	Compartment ratios			
	Milk : Plasma	Plasma : Brain	Plasma : Plasma	Brain : Brain
Dam	3-6 : 1	6-7 : 1	-	-
Pup	-	1-2 : 1	-	-
Pup : Dam	-	-	1-3 : 1	5-7 : 1
Dam : Pup	1-4 : 1	-	-	-

a Data were obtained from page 31 of MRID 46727401.

APPENDIX 3

TABLE 22 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 14 - F1 ANIMALS

MALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	41.3	46.2	37.9	37.7
	S.D.	27.4	28.6	26.2	24.0
	N	12	12	14	14
Minutes 6-10	Mean	23.8	32.6	14.9	32.9
	S.D.	16.4	25.2	16.0	21.9
	N	12	12	14	14
Minutes 11-15	Mean	23.2	37.7	29.7	29.2
	S.D.	18.5	25.2	20.1	20.4
	N	12	12	14	14
Minutes 16-20	Mean	29.0	37.7	18.8	26.8
	S.D.	19.6	29.0	23.3	18.5
	N	12	12	14	14
Minutes 21-25	Mean	16.9	19.5	10.6	23.3
	S.D.	15.5	18.0	15.8	18.8
	N	12	12	14	14
Minutes 26-30	Mean	24.8	21.9	16.6	14.1
	S.D.	26.6	24.6	21.8	15.9
	N	12	12	14	14
Minutes 31-35	Mean	24.5	19.1	11.9	5.3**
	S.D.	25.5	23.0	11.8	9.2
	N	12	12	14	14
Minutes 36-40	Mean	17.7	9.3	16.9	6.7
	S.D.	18.8	14.7	23.0	11.9
	N	12	12	14	14
Minutes 41-45	Mean	9.6	5.0	8.9	9.2
	S.D.	11.7	7.0	15.7	12.7
	N	12	12	14	14
Minutes 46-50	Mean	20.7	5.1*	9.6	7.7*
	S.D.	18.4	7.7	18.5	13.3
	N	12	12	14	14
Overall (1-50)	Mean	231.5	234.0	175.6	193.0
	S.D.	126.8	128.1	82.2	103.8
	N	12	12	14	14

TABLE 22 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 14 - F1 ANIMALS

		Dose level of Abamectin (mg/kg/day)			
FEMALES		0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	49.7	51.4	37.6	39.0
	S.D.	31.7	29.6	25.5	28.3
	N	12	12	15	13
Minutes 6-10	Mean	28.2	34.2	21.5	23.7
	S.D.	22.5	28.9	19.3	28.4
	N	12	12	15	13
Minutes 11-15	Mean	17.8	31.1	21.7	20.5
	S.D.	17.7	28.7	21.7	13.8
	N	12	12	15	13
Minutes 16-20	Mean	22.9	19.0	17.9	21.0
	S.D.	24.6	24.9	18.1	21.9
	N	12	12	15	13
Minutes 21-25	Mean	13.8	20.4	19.6	8.4
	S.D.	19.9	28.8	23.5	9.9
	N	12	12	15	13
Minutes 26-30	Mean	10.3	8.4	10.3	4.5
	S.D.	14.7	10.4	17.5	10.1
	N	12	12	15	13
Minutes 31-35	Mean	8.9	14.8	10.9	10.4
	S.D.	12.0	21.5	16.6	13.4
	N	12	12	15	13
Minutes 36-40	Mean	4.9	9.3	9.9	12.8
	S.D.	6.9	11.8	14.7	16.1
	N	12	12	15	13
Minutes 41-45	Mean	7.3	7.3	14.3	6.4
	S.D.	18.3	13.4	18.6	10.2
	N	12	12	15	13
Minutes 46-50	Mean	2.8	6.2	10.7	4.2
	S.D.	5.4	6.9	19.2	8.5
	N	12	12	15	13
Overall (1-50)	Mean	166.7	202.0	174.3	150.9
	S.D.	105.8	134.3	131.4	103.2
	N	12	12	15	13

TABLE 23 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 18 - F1 ANIMALS

		Dose level of Abamectin (mg/kg/day)			
MALES		0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	28.1	26.1	22.9	17.6
	S.D.	24.6	30.8	19.5	20.2
	N	12	12	14	14
Minutes 6-10	Mean	23.3	23.9	15.4	17.4
	S.D.	22.4	36.6	19.0	25.3
	N	12	12	14	14
Minutes 11-15	Mean	21.9	18.1	15.4	19.7
	S.D.	16.9	25.0	16.8	24.9
	N	12	12	14	14
Minutes 16-20	Mean	15.4	14.5	12.4	14.8
	S.D.	19.6	27.6	20.5	22.3
	N	12	12	14	14
Minutes 21-25	Mean	14.2	11.8	11.9	16.4
	S.D.	19.8	30.6	16.5	27.2
	N	12	12	14	14
Minutes 26-30	Mean	18.3	11.7	12.6	8.8
	S.D.	22.4	27.3	18.0	18.0
	N	12	12	14	14
Minutes 31-35	Mean	10.6	20.6	8.4	5.9
	S.D.	15.5	31.9	14.5	11.0
	N	12	12	14	14
Minutes 36-40	Mean	13.1	10.9	5.1	6.1
	S.D.	19.1	13.5	14.5	13.5
	N	12	12	14	14
Minutes 41-45	Mean	10.0	10.3	5.8	7.5
	S.D.	18.7	16.4	11.8	14.6
	N	12	12	14	14
Minutes 46-50	Mean	13.2	14.9	3.8	9.9
	S.D.	20.4	22.2	8.6	15.0
	N	12	12	14	14
Overall (1-50)	Mean	168.0	162.8	113.7	124.1
	S.D.	157.3	210.8	106.3	143.9
	N	12	12	14	14

TABLE 23 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 18 - F1 ANIMALS

		Dose level of Abamectin (mg/kg/day)			
FEMALES		0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	23.9	22.1	25.3	22.7
	S.D.	16.6	26.0	20.1	19.2
	N	12	12	15	13
Minutes 6-10	Mean	28.9	24.6	16.0	18.2
	S.D.	14.0	24.1	20.9	20.4
	N	12	12	15	13
Minutes 11-15	Mean	23.9	20.8	9.0	13.2
	S.D.	18.9	27.3	14.2	18.0
	N	12	12	15	13
Minutes 16-20	Mean	15.1	15.6	11.2	18.8
	S.D.	17.8	20.7	19.9	21.6
	N	12	12	15	13
Minutes 21-25	Mean	11.8	15.7	11.7	11.8
	S.D.	14.3	17.6	18.6	18.7
	N	12	12	15	13
Minutes 26-30	Mean	17.6	11.6	5.8	16.6
	S.D.	20.2	18.2	12.5	19.5
	N	12	12	15	13
Minutes 31-35	Mean	13.9	9.9	7.2	13.7
	S.D.	16.7	15.4	16.0	19.1
	N	12	12	15	13
Minutes 36-40	Mean	2.7	8.3	5.5	13.4*
	S.D.	4.2	10.4	13.2	17.9
	N	12	12	15	13
Minutes 41-45	Mean	13.1	11.6	3.9	12.3
	S.D.	23.3	16.7	8.5	17.7
	N	12	12	15	13
Minutes 46-50	Mean	9.9	12.0	9.3	13.8
	S.D.	18.9	21.1	19.3	24.2
	N	12	12	15	13
Overall (1-50)	Mean	160.8	152.2	104.9	154.6
	S.D.	93.4	141.7	116.9	144.3
	N	12	12	15	13

TABLE 24 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 22 - F1 ANIMALS

		Dose level of Abamectin (mg/kg/day)			
MALES		0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	41.3	44.9	36.6	33.9
	S.D.	18.6	26.0	21.1	22.7
	N	12	12	14	14
Minutes 6-10	Mean	33.1	47.8	30.2	26.1
	S.D.	21.7	32.6	21.9	22.7
	N	12	12	14	14
Minutes 11-15	Mean	28.3	29.7	27.3	26.8
	S.D.	20.1	29.6	21.8	22.5
	N	12	12	14	14
Minutes 16-20	Mean	31.4	29.5	19.7	30.3
	S.D.	22.0	20.2	23.3	25.4
	N	12	12	14	14
Minutes 21-25	Mean	26.8	29.4	25.7	28.6
	S.D.	27.7	18.9	27.2	22.7
	N	12	12	14	14
Minutes 26-30	Mean	37.6	27.1	33.9	39.8
	S.D.	27.0	26.7	27.2	24.3
	N	12	12	14	14
Minutes 31-35	Mean	33.6	26.7	39.4	38.9
	S.D.	24.0	23.3	23.0	18.5
	N	12	12	14	14
Minutes 36-40	Mean	33.5	26.5	28.6	31.1
	S.D.	22.4	24.3	25.5	25.1
	N	12	12	14	14
Minutes 41-45	Mean	30.8	25.8	32.4	20.6
	S.D.	25.7	19.4	22.0	22.9
	N	12	12	14	14
Minutes 46-50	Mean	25.7	31.8	29.6	34.9
	S.D.	16.8	26.8	26.5	26.4
	N	12	12	14	14
Overall (1-50)	Mean	322.1	319.1	303.4	310.9
	S.D.	178.7	202.6	172.3	150.3
	N	12	12	14	14

TABLE 24 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 22 - F1 ANIMALS

		Dose level of Abamectin (mg/kg/day)			
FEMALES		0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	41.5	36.2	42.3	40.1
	S.D.	18.8	22.9	20.1	20.4
	N	12	12	15	13
Minutes 6-10	Mean	38.9	38.8	35.9	39.5
	S.D.	24.6	26.5	22.0	22.8
	N	12	12	15	13
Minutes 11-15	Mean	29.5	36.8	27.7	34.5
	S.D.	19.8	28.5	22.5	23.8
	N	12	12	15	13
Minutes 16-20	Mean	32.0	27.4	28.4	29.4
	S.D.	20.1	25.4	20.5	27.0
	N	12	12	15	13
Minutes 21-25	Mean	36.0	31.4	31.2	29.0
	S.D.	23.6	23.9	18.6	21.6
	N	12	12	15	13
Minutes 26-30	Mean	28.6	29.4	37.0	34.9
	S.D.	19.7	19.9	14.9	27.1
	N	12	12	15	13
Minutes 31-35	Mean	38.1	20.6*	38.3	35.3
	S.D.	22.0	13.6	22.6	23.8
	N	12	12	15	13
Minutes 36-40	Mean	31.7	16.8	36.9	22.5
	S.D.	22.9	12.0	16.9	24.5
	N	12	12	15	13
Minutes 41-45	Mean	26.5	28.0	36.3	32.2
	S.D.	22.5	20.2	15.7	25.8
	N	12	12	15	13
Minutes 46-50	Mean	29.8	25.8	38.8	27.3
	S.D.	17.7	27.1	21.0	25.3
	N	12	12	15	13
Overall (1-50)	Mean	332.5	291.3	352.7	324.5
	S.D.	156.3	161.5	108.7	155.0
	N	12	12	15	13

TABLE 25 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 60 - F1 ANIMALS

MALES		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	62.7	67.1	65.6	61.8
	S.D.	11.0	7.7	9.5	10.0
	N	10	10	11	11
Minutes 6-10	Mean	63.1	68.8	65.0	64.7
	S.D.	12.1	11.2	4.5	10.2
	N	10	10	11	11
Minutes 11-15	Mean	54.3	59.9	58.3	55.8
	S.D.	11.1	15.5	15.0	21.4
	N	10	10	11	11
Minutes 16-20	Mean	43.4	44.6	51.3	53.3
	S.D.	27.2	23.8	18.5	13.4
	N	10	10	11	11
Minutes 21-25	Mean	37.4	33.8	47.4	44.5
	S.D.	25.7	27.1	22.0	19.6
	N	10	10	11	11
Minutes 26-30	Mean	33.2	49.3	44.3	31.0
	S.D.	23.6	22.6	22.3	24.1
	N	10	10	11	11
Minutes 31-35	Mean	43.4	36.1	48.6	36.5
	S.D.	30.5	32.2	25.5	28.3
	N	10	10	11	11
Minutes 36-40	Mean	46.9	32.4	42.1	37.1
	S.D.	21.4	31.4	31.4	24.9
	N	10	10	11	11
Minutes 41-45	Mean	54.4	37.9	37.6	45.2
	S.D.	21.1	32.8	30.3	20.6
	N	10	10	11	11
Minutes 46-50	Mean	48.2	32.7	34.1	44.5
	S.D.	21.2	31.7	29.3	23.1
	N	10	10	11	11
Overall (1-50)	Mean	487.0	462.6	494.3	474.5
	S.D.	149.6	179.5	164.1	115.7
	N	10	10	11	11

TABLE 25 INTERGROUP COMPARISON OF MOTOR ACTIVITY DAY 60 - F1 ANIMALS

		Dose level of Abamectin (mg/kg/day)			
FEMALES		0(Control)	0.12	0.20	0.40
Minutes 1-5	Mean	59.0	60.8	64.5	62.2
	S.D.	11.8	6.8	11.6	6.2
	N	10	10	12	11
Minutes 6-10	Mean	60.1	55.5	68.0	61.9
	S.D.	9.9	9.6	9.6	9.4
	N	10	10	12	11
Minutes 11-15	Mean	61.5	61.9	66.8	59.6
	S.D.	11.6	12.1	10.6	10.9
	N	10	10	12	11
Minutes 16-20	Mean	59.0	50.5	58.2	64.1
	S.D.	22.2	20.9	17.7	7.6
	N	10	10	12	11
Minutes 21-25	Mean	46.6	53.2	52.8	56.5
	S.D.	22.1	19.3	16.8	8.0
	N	10	10	12	11
Minutes 26-30	Mean	51.2	46.6	55.6	51.1
	S.D.	25.6	24.8	22.1	12.7
	N	10	10	12	11
Minutes 31-35	Mean	54.7	45.7	57.4	51.8
	S.D.	15.0	25.4	24.9	13.9
	N	10	10	12	11
Minutes 36-40	Mean	53.9	48.2	61.7	47.0
	S.D.	18.3	19.6	23.7	14.3
	N	10	10	12	11
Minutes 41-45	Mean	59.3	50.9	59.8	61.8
	S.D.	13.7	24.0	17.5	8.5
	N	10	10	12	11
Minutes 46-50	Mean	58.2	43.9	59.2	55.2
	S.D.	16.0	25.4	18.5	9.6
	N	10	10	12	11
Overall (1-50)	Mean	563.5	517.2	603.8	571.2
	S.D.	107.5	117.2	129.0	43.6
	N	10	10	12	11

APPENDIX 4

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 24 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 3 sec	Mean	20.1	23.6	24.7	23.5
	S.D.	22.0	24.5	23.0	20.8
	N	24	24	29	27
Cut-off 4 sec	Mean	35.4	47.9	44.3	40.7
	S.D.	23.7	24.2	27.6	23.7
	N	24	24	29	27
Cut-off 5 sec	Mean	40.3	55.6*	54.0*	51.9
	S.D.	23.0	22.3	23.4	20.8
	N	24	24	29	27
Cut-off 6 sec	Mean	49.3	62.5*	59.2	61.1
	S.D.	24.3	21.0	25.0	21.7
	N	24	24	29	27
Cut-off 7 sec	Mean	59.0	68.8	65.5	64.8
	S.D.	22.5	18.6	25.6	21.4
	N	24	24	29	27
Cut-off 8 sec	Mean	63.9	77.8*	70.7	70.4
	S.D.	20.1	12.7	21.2	21.8
	N	24	24	29	27
Cut-off 9 sec	Mean	68.8	79.9*	74.1	77.2*
	S.D.	20.4	13.0	18.1	21.8
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 24 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 10 sec	Mean	76.4	81.3	75.9	80.9
	S.D.	12.9	12.3	18.7	20.0
	N	24	24	29	27
Cut-off 1.0xstraight channel	Mean	10.4	21.5	25.9*	17.9
	S.D.	20.2	30.5	28.7	29.6
	N	24	24	29	27
Cut-off 1.5xstraight channel	Mean	34.0	47.9	48.3	47.5
	S.D.	24.3	27.9	28.3	31.6
	N	24	24	29	27
Cut-off 2.0xstraight channel	Mean	47.9	61.8	58.6	58.0
	S.D.	21.6	21.1	25.0	27.1
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 24 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 3 sec	Mean	22.9	22.2	13.2	25.3
	S.D.	21.5	19.5	20.1	24.6
	N	24	24	29	27
Cut-off 4 sec	Mean	42.4	41.0	34.5	44.4
	S.D.	25.5	21.4	20.4	27.0
	N	24	24	29	27
Cut-off 5 sec	Mean	47.9	47.9	46.0	52.5
	S.D.	22.7	22.2	18.2	24.3
	N	24	24	29	27
Cut-off 6 sec	Mean	52.8	52.1	52.3	58.0
	S.D.	23.4	22.2	21.7	23.7
	N	24	24	29	27
Cut-off 7 sec	Mean	56.3	58.3	60.9	63.0
	S.D.	21.3	23.6	21.0	23.7
	N	24	24	29	27
Cut-off 8 sec	Mean	59.7	64.6	66.1	67.3
	S.D.	20.2	22.7	20.2	22.9
	N	24	24	29	27
Cut-off 9 sec	Mean	64.6	64.6	72.4	72.2
	S.D.	19.2	22.7	16.8	20.7
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 24 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 10 sec	Mean	66.7	68.8	75.9	75.3
	S.D.	19.7	20.4	16.4	20.3
	N	24	24	29	27
Cut-off 1.0xstraight channel	Mean	13.2	18.8	25.3	18.5
	S.D.	19.6	20.4	29.4	22.8
	N	24	24	29	27
Cut-off 1.5xstraight channel	Mean	47.2	44.4	43.7	42.6
	S.D.	26.3	24.9	26.5	27.9
	N	24	24	29	27
Cut-off 2.0xstraight channel	Mean	55.6	53.5	58.0	56.8
	S.D.	23.9	24.6	23.8	24.1
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 27 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 3 sec	Mean	43.1	34.7	31.0	37.0
	S.D.	25.0	22.5	22.6	25.0
	N	24	24	29	27
Cut-off 4 sec	Mean	60.4	49.3	50.0	53.1
	S.D.	23.5	23.8	23.6	22.2
	N	24	24	29	27
Cut-off 5 sec	Mean	64.6	61.8	59.2	66.0
	S.D.	23.7	21.1	19.7	18.2
	N	24	24	29	27
Cut-off 6 sec	Mean	70.1	72.2	66.7	74.7
	S.D.	25.5	14.5	19.9	16.3
	N	24	24	29	27
Cut-off 7 sec	Mean	75.0	82.6	73.6	80.2
	S.D.	23.1	15.9	21.6	15.4
	N	24	24	29	27
Cut-off 8 sec	Mean	77.8	87.5	78.2	84.6
	S.D.	22.3	12.3	18.4	14.6
	N	24	24	29	27
Cut-off 9 sec	Mean	80.6	89.6	83.9	89.5*
	S.D.	20.7	12.8	16.4	14.0
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 27 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 10 sec	Mean	86.1	91.0	87.4	91.4
	S.D.	17.5	11.0	15.2	12.5
	N	24	24	29	27
Cut-off 1.0xstraight channel	Mean	29.9	38.9	28.7	34.0
	S.D.	35.4	27.7	32.1	32.8
	N	24	24	29	27
Cut-off 1.5xstraight channel	Mean	63.2	65.3	57.5	63.0
	S.D.	29.9	25.5	26.2	23.3
	N	24	24	29	27
Cut-off 2.0xstraight channel	Mean	72.2	75.0	71.8	77.2
	S.D.	25.9	19.7	22.3	19.1
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 27 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 3 sec	Mean	33.3	43.1	37.9	46.3
	S.D.	22.5	24.0	22.7	23.3
	N	24	24	29	27
Cut-off 4 sec	Mean	52.8	56.9	52.3	63.0
	S.D.	23.9	21.9	23.5	20.8
	N	24	24	29	27
Cut-off 5 sec	Mean	61.8	61.8	66.1	69.8
	S.D.	24.8	21.7	17.0	18.5
	N	24	24	29	27
Cut-off 6 sec	Mean	71.5	66.7	72.4	74.1
	S.D.	21.1	20.9	15.0	17.5
	N	24	24	29	27
Cut-off 7 sec	Mean	76.4	77.1	78.7	79.6
	S.D.	21.9	18.9	14.7	14.9
	N	24	24	29	27
Cut-off 8 sec	Mean	79.9	80.6	83.9	84.0
	S.D.	20.8	17.5	12.2	9.8
	N	24	24	29	27
Cut-off 9 sec	Mean	84.7	83.3	85.6	86.4
	S.D.	20.2	15.5	13.2	10.4
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 27 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 10 sec	Mean	86.8	87.5	87.9	89.5
	S.D.	16.3	15.7	12.5	11.5
	N	24	24	29	27
Cut-off 1.0xstraight channel	Mean	34.7	25.0	25.9	26.5
	S.D.	28.6	29.1	29.4	30.0
	N	24	24	29	27
Cut-off 1.5xstraight channel	Mean	59.7	57.6	59.8	56.8
	S.D.	26.4	26.9	22.9	25.0
	N	24	24	29	27
Cut-off 2.0xstraight channel	Mean	68.8	66.0	73.6	71.0
	S.D.	25.2	25.8	20.7	16.4
	N	24	24	29	27

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 59 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 3 sec	Mean	33.3	36.8	28.6	35.9
	S.D.	26.9	26.5	24.8	24.4
	N	24	24	28	26
Cut-off 4 sec	Mean	59.7	59.0	58.3	51.3
	S.D.	19.0	24.6	17.3	23.1
	N	24	24	28	26
Cut-off 5 sec	Mean	67.4	69.4	63.1	64.1
	S.D.	13.4	16.8	15.3	20.4
	N	24	24	28	26
Cut-off 6 sec	Mean	74.3	76.4	69.6	70.5
	S.D.	9.8	14.7	15.7	18.4
	N	24	24	28	26
Cut-off 7 sec	Mean	79.2	81.3	75.6	80.8
	S.D.	13.2	13.3	16.0	18.7
	N	24	24	28	26
Cut-off 8 sec	Mean	82.6	84.7	79.2	84.6
	S.D.	11.5	14.7	14.1	16.9
	N	24	24	28	26
Cut-off 9 sec	Mean	88.2	87.5	83.9	88.5
	S.D.	11.5	14.1	13.2	14.0
	N	24	24	28	26

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 59 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 10 sec	Mean	91.0	89.6	89.3	90.4
	S.D.	9.8	12.8	12.2	12.6
	N	24	24	28	26
Cut-off 1.0xstraight channel	Mean	20.1	15.3	19.6	19.2
	S.D.	27.4	20.2	30.4	22.5
	N	24	24	28	26
Cut-off 1.5xstraight channel	Mean	56.3	53.5	52.4	51.9
	S.D.	21.9	26.5	27.5	23.7
	N	24	24	28	26
Cut-off 2.0xstraight channel	Mean	69.4	67.4	65.5	60.3
	S.D.	16.8	17.4	19.2	23.1
	N	24	24	28	26

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 59 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 3 sec	Mean	31.8	37.7	20.7	32.7
	S.D.	23.5	25.2	20.6	26.9
	N	22	23	25	26
Cut-off 4 sec	Mean	53.0	51.4	44.0	55.8
	S.D.	20.3	23.5	22.5	26.2
	N	22	23	25	26
Cut-off 5 sec	Mean	61.4	59.4	56.7	60.9
	S.D.	18.1	20.6	15.2	25.8
	N	22	23	25	26
Cut-off 6 sec	Mean	65.9	69.6	63.3	66.7
	S.D.	17.4	17.9	13.6	18.9
	N	22	23	25	26
Cut-off 7 sec	Mean	68.9	74.6	68.7	73.1
	S.D.	17.3	16.6	13.0	17.7
	N	22	23	25	26
Cut-off 8 sec	Mean	73.5	77.5	73.3	76.9
	S.D.	16.0	17.8	13.6	16.4
	N	22	23	25	26
Cut-off 9 sec	Mean	78.0	84.8	79.3	78.8
	S.D.	14.9	15.0	12.1	14.6
	N	22	23	25	26

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 59 (LEARNING PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 10 sec	Mean	84.1	89.9	84.0	84.0
	S.D.	10.9	10.9	12.2	10.0
	N	22	23	25	26
Cut-off 1.0xstraight channel	Mean	22.0	19.6	24.0	24.4
	S.D.	26.4	25.5	28.5	28.4
	N	22	23	25	26
Cut-off 1.5xstraight channel	Mean	49.2	52.2	48.7	52.6
	S.D.	22.7	26.7	26.8	23.9
	N	22	23	25	26
Cut-off 2.0xstraight channel	Mean	62.1	58.7	64.7	67.3
	S.D.	18.7	26.0	21.1	19.7
	N	22	23	25	26

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 62 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 3 sec	Mean	23.6	34.0	20.8	34.6
	S.D.	25.5	27.1	24.3	26.2
	N	24	24	28	26
Cut-off 4 sec	Mean	38.9	52.8	40.5	56.4*
	S.D.	25.9	27.2	27.8	27.9
	N	24	24	28	26
Cut-off 5 sec	Mean	49.3	56.9	49.4	67.3*
	S.D.	28.4	24.5	27.4	25.6
	N	24	24	28	26
Cut-off 6 sec	Mean	54.9	66.7	63.1	74.4*
	S.D.	28.0	24.6	25.4	24.1
	N	24	24	28	26
Cut-off 7 sec	Mean	62.5	73.6	72.6	78.8*
	S.D.	27.5	21.4	21.9	22.9
	N	24	24	28	26
Cut-off 8 sec	Mean	68.8	77.8	77.4	86.5**
	S.D.	27.5	22.3	21.4	18.9
	N	24	24	28	26
Cut-off 9 sec	Mean	73.6	80.6	83.9	87.2*
	S.D.	25.0	21.8	15.4	19.0
	N	24	24	28	26

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 62 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
MALES					
Cut-off 10 sec	Mean	79.2	82.6	89.3	89.1
	S.D.	22.1	20.0	13.0	16.3
	N	24	24	28	26
Cut-off 1.0xstraight channel	Mean	14.6	14.6	6.0	17.3
	S.D.	25.2	19.2	15.9	25.2
	N	24	24	28	26
Cut-off 1.5xstraight channel	Mean	41.0	44.4	32.7	51.3
	S.D.	31.8	24.9	27.8	32.6
	N	24	24	28	26
Cut-off 2.0xstraight channel	Mean	53.5	56.3	48.2	64.7
	S.D.	29.9	24.5	28.5	26.0
	N	24	24	28	26

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 62 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 3 sec	Mean	31.1	32.6	18.7	31.4
	S.D.	25.9	30.8	20.6	26.4
	N	22	23	25	26
Cut-off 4 sec	Mean	45.5	41.3	37.3	44.2
	S.D.	21.9	29.7	23.2	22.6
	N	22	23	25	26
Cut-off 5 sec	Mean	55.3	52.2	52.7	55.8
	S.D.	20.8	23.2	20.2	23.5
	N	22	23	25	26
Cut-off 6 sec	Mean	62.1	61.6	63.3	60.9
	S.D.	20.7	23.3	22.6	23.1
	N	22	23	25	26
Cut-off 7 sec	Mean	67.4	66.7	71.3	66.0
	S.D.	18.2	20.7	21.8	25.6
	N	22	23	25	26
Cut-off 8 sec	Mean	72.0	71.0	74.0	71.8
	S.D.	14.0	20.9	19.9	25.3
	N	22	23	25	26
Cut-off 9 sec	Mean	78.0	73.2	80.0	78.2
	S.D.	15.8	21.8	18.0	22.0
	N	22	23	25	26

A successful trial is one completed in less than the cut-off time

TABLE 29 INTERGROUP COMPARISON OF THE PROPORTION OF SUCCESSFUL TRIALS - F1 ANIMALS

DAY 62 (MEMORY PHASE)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
FEMALES					
Cut-off 10 sec	Mean	83.3	76.8	81.3	81.4
	S.D.	13.6	18.6	17.6	21.3
	N	22	23	25	26
Cut-off 1.0xstraight channel	Mean	10.6	15.2	10.7	12.8
	S.D.	20.3	21.9	20.9	20.2
	N	22	23	25	26
Cut-off 1.5xstraight channel	Mean	49.2	43.5	38.7	44.2
	S.D.	22.7	27.4	28.3	26.6
	N	22	23	25	26
Cut-off 2.0xstraight channel	Mean	59.8	55.1	54.7	54.5
	S.D.	24.5	26.8	25.2	26.9
	N	22	23	25	26

A successful trial is one completed in less than the cut-off time

APPENDIX 5

TABLE 32 INTERGROUP COMPARISON OF BRAIN (PERFUSED) WEIGHTS DAY 63 - F1 ANIMALS

BRAIN (POST-PERFUSION)		Dose level of Abamectin (mg/kg/day) 0(Control)	0.12	0.20	0.40
Males					
Terminal Bodyweight (g)	Mean	349.4	353.8	338.5	331.4
	S.D.	18.0	21.8	18.4	20.9
	N	12	12	14	14
Brain Weight (g)	Mean	2.05	2.04	2.06	1.98
	S.D.	0.12	0.14	0.08	0.08
	N	12	12	14	14
#Brain Weight to Bodyweight Ratio (%)	Mean	0.59	0.58	0.61	0.60
	S.D.	0.04	0.04	0.03	0.05
	N	12	12	14	14
Brain Weight Adjusted For Bodyweight		2.04	2.03	2.06	1.99
Females					
Terminal Bodyweight (g)	Mean	220.1	216.7	203.2	195.2
	S.D.	17.3	17.2	20.0	14.2
	N	12	12	15	13
Brain Weight (g)	Mean	1.92	1.93	1.88	1.92
	S.D.	0.08	0.07	0.09	0.06
	N	12	12	15	13
#Brain Weight to Bodyweight Ratio (%)	Mean	0.87	0.90	0.93	0.99
	S.D.	0.05	0.08	0.08	0.06
	N	12	12	15	13
Brain Weight Adjusted For Bodyweight		1.89	1.91	1.89	1.94

no statistical analysis of organ to bodyweight ratios performed

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